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HEURISTIC GLIMPSES INTO THE EVOLUTION OF RADIATION THERAPY*

PARTICULARLY IN REFERENCE TO GYNECOLOGIC CANCERS CALDWELL LECTURE, 1960

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At the threshold of the fifth decade of a brilliant series of annual lectures given in memory of Doctor Eugene Caldwell, it is with a sense of deep humility and understandable timidity that I rise to give the fortieth lecture.

Dr. Caldwell died a martyr in 1918, at the time when the precisely regulated incandescence of the tungsten cathode of a therapeutic roentgen ray tube became a reality. Although his contributions were greatest to diagnostic radiology, he also devised in 1902 a treatment tube for insertion into body cavities and continued to maintain a keen interest in the development and improvement of other types of tubes applicable to therapeutic radiology. As an electrical engineer and physicist at the beginning and as a physician later, he was a technical perfectionist, a great creative genius, and above all an inspirational idealist. In severe self-criticism he said of himself:[25] "One must necessarily make statements which are more or less dogmatic and in which the 'personal equation' is an important factor." Personal equations are attributes of true pioneers who in their never flagging zeal leave indelible impressions upon their successors. The American Roentgen Ray Society has a long list of dauntless pioneers, many of whom became martyrs. The name of Eugene Caldwell, in a way, has become a symbol of their zeal, perseverance and faith.

I am profoundly grateful to Dr. Reineke for the honor of having been chosen to give this fortieth lecture. I am also indebted to Dr. Reineke for accepting my topic of this evening, for, in view of the rapidly expanding interest in radiation therapy, this affords me the opportunity for some heuristic glimpses into its evolution, from the era of the "cranky" apple-green gas tubes to the present era of modern equipment and precision technology.

"HEURISTIC," serving to find out, has become an expression for a method of investigation that aids in the discovery or interpretation of facts and truths ever since the Greek philosopher, Archimedes, exclaimed, "Eureka!" in his elation at discovering the now universally known Archimedean principle. The comparatively young science of radiology and more particularly the science of radiation therapy has, as no other branch of medicine, encountered formidable difficulties in its slow rhythmic evolution. The necessity

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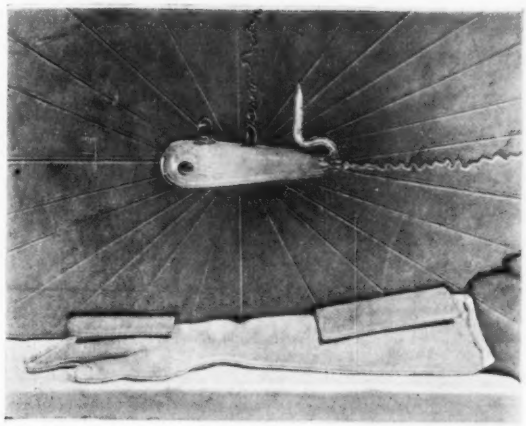
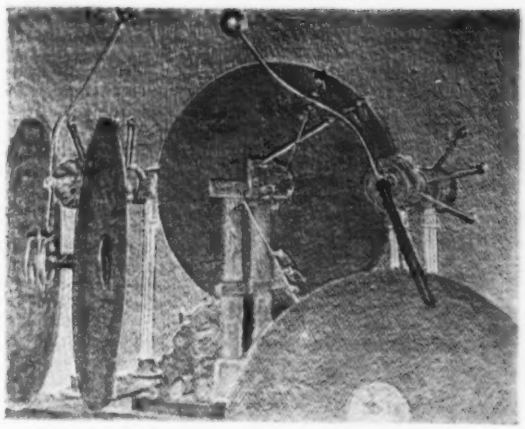
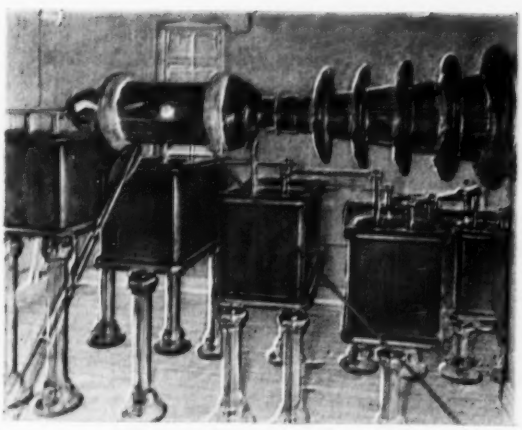
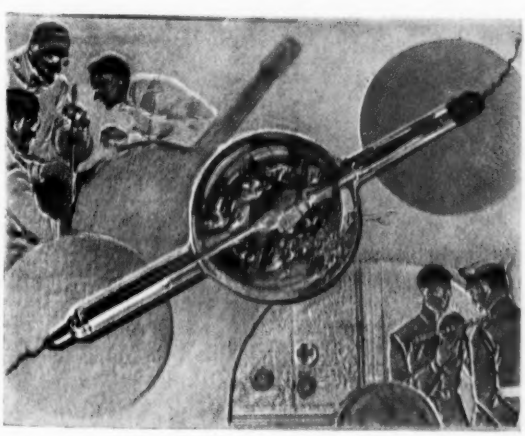
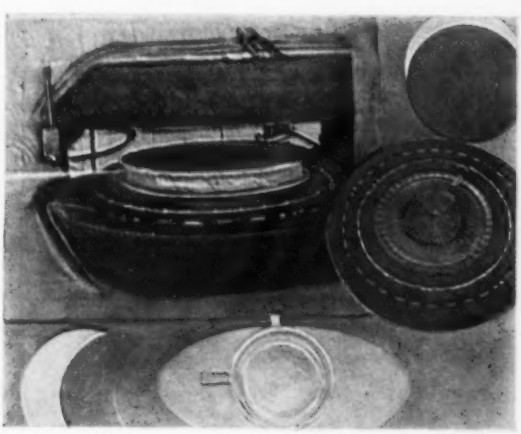
of relying on rays, whether they be vibratory or particulate, which cannot be seen by the naked eye, the extremely complex ways by which these rays are produced, measured physically and assayed in their biologic action, and the determination of their true place among other, considerably older, treatment methods constituted problems which could be approached only in the light of contemporary technical and medical achievements. Some of these problems have been successfully solved, others—still too perplexing—continue to form a tempting challenge to the inquiring mind. Such a problem is a study of the salient phases influencing most profoundly the development of radiation therapy and thereby establishing its usefulness in the treatment of the large group of gynecologic cancers. Heuristic glimpses into the discoveries of the time may help in properly interpreting the facts resulting from these discoveries.

As was to be expected, in the beginning, soon after the discovery in 1895 by Röntgen of the "invisible ray" which was to illuminate the medical world, treatment with this new kind of ray was acclaimed with enthusiasm. The memorable discoveries which Finsen made with ultraviolet rays at the turn of the century had a marked effect also on radiation therapy especially in the dermatologic field, where it was first applied. Since it was necessary that the Finsen ultraviolet rays produce, for therapeutic effect, "a reaction which may vary in degree from an erythema to a vesicular or bullous dermatitis," it was assumed that a similar reaction ought to be produced by roentgen rays. The importance of this reaction, which was variously called "x-ray inflammation" or "x-ray burn," was emphasized by practically all the radiotherapists at that time. To quote Rinehart:[26,27] "The method employed was to cover the healthy skin with thin sheet lead, and to expose the sore or part to be treated for five minutes at 8 inches the first day, increasing the time of exposure and shortening the distance each day until a decided inflammatory reaction was obtained, a low vacuum tube giving a soft green light being used. I have been unable to obtain any benefit in any case of the kind without an inflammatory reaction." The voltage range which usually was expressed in spark-gap distance was low, varying from 50 to 100 kv. Because of the lack of penetration of the roentgen rays and the fact that they were used for treatment of lesions lying on the surface or near the surface of the skin, the term "superficial roentgen therapy" was later coined for this form of treatment. By 1904, it had found such widespread use that Professor Brocq of the Hôpital Broca of Paris, in a preface to J. Belot's treatise on *Radiotherapy*, wrote: "Radiology was born but yesterday; it has already made enormous strides. To-day it may be said to dominate the therapeutics of dermatology."

Although the risk of a "deep burn in hope of quickly destroying the tumour" was justifiable in the treatment of skin cancer and other malignant neoplasms, the production of "x-ray inflammation" for the treatment of many benign conditions, together with the vagaries of the machines used, led to some unexpected and often disastrous results. Thus, the period of great enthusiasm was followed by a period of even greater pessimism. To quote Mac Kee:[22] "The failure to substantiate the early therapeutic results, the injurious effects observed as time went on, and the fact that there was no satisfactory method of estimating or of controlling the quantity and quality of radiation administered resulted in a period of depression or pessimism which endured from about 1906 to about 1912." A perusal of the literature during this period is replete with recitals of cases of "severe x-ray burns" and "a few deaths" and A. R. Robinson[28] in the October 6, 1906 issue of the *British Medical Journal* made the statement: "The roentgen rays have been far too widely employed, almost justifying their designation as race suicide machines."

In 1910, Kassabian[17] wrote: "With the employment of the roentgen rays for thera-

Composite bas-relief mural tableaux based on contemporary photographs, sketches and etchings (Harper Hospital).

peutic purposes, burns have now become a common accident. In several instances suits were brought against physicians on the ground that they did not use the necessary means of protection; in most of these cases the severe character of the diseases demanded so severe a treatment that burning had to be contended with." Dr. Kassabian in the very same year became himself a martyr to roentgen injuries due to this lack of protection. His list of physicians who were sued contained some of the prominent names of the time both from this country and Europe.

During this most discouraging phase in the evolution of radiation therapy, Dr. Hickey,[12] Founder and first Editor of this JOURNAL, journeyed to New York to personally witness a preliminary demonstration given Saturday evening, December 27, 1913, at the Hotel St. Denis of a new form of roentgen tube, invented by Dr. Coolidge[6] of Schenectady, honorary member of this Society. In an inspired editorial, Dr. Hickey immediately announced this epoch-making event to the world with the statement: "This contribution to roentgenology is, in the words of Prof. Shearer of Cornell University, the most important which American genius has ever offered." At the time of demonstration, the therapeutic value of the tube was wholly untried, but Dr. Hickey conjectured that "owing to the extreme exhaustion, penetrating rays of the therapeutic value of the gamma rays of radium may be produced. This, of course, opens up the most wonderful new possibilities for treatment."

The progress that followed was swift. The development of a suitable high voltage energizing source for operation of the new tube, continuous improvements in design of its electron emissivity, the introduction of autotransformer control of the primary voltage and proper rectification of the secondary voltage paved the way, as clinical therapy moved forward in great strides.[7,8] Superficial roentgen therapy (50–130 kv.) at once emerged from its era of pessimism, and since 1914, to again quote Mac Kee[22] has "stood the test of time," thus inaugurating a period of "realism;" medium roentgen therapy (130–170 kv.) was laid on a sounder foundation.

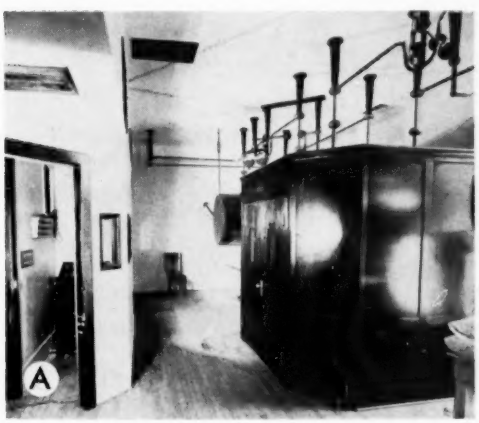
This swift progress provided the American Expeditionary Forces in World War I with the best equipment up to that time[18] and it was the good fortune of my distinguished mentor of this evening, young Captain Lawrence Reynolds, to be the recipient at the American Ambulance Hospital No. 1, later called the American Military Hospital No. 1, of the first Coolidge tube overseas. This tube was presented for inspection to General Pershing himself on his visit to the hospital.

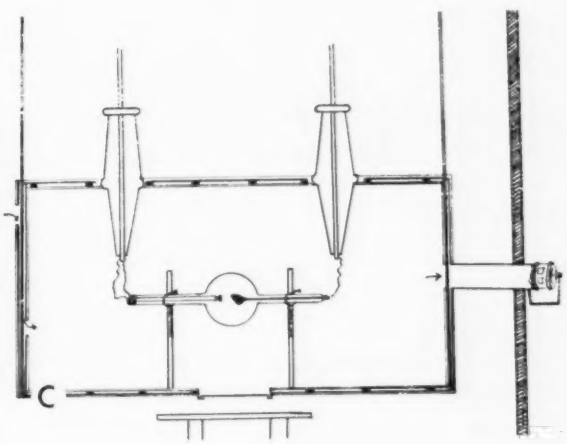
It may be said that the introduction of the Coolidge tube has revolutionized therapeutic radiology. Its range was rapidly extended to 200 kv., establishing in the early 1920's the solid basis of deep roentgen therapy or, as we now prefer to call it following the suggestion of Dr. Garland, orthovoltage roentgen therapy. This form of treatment gave such impetus to the clinical application of radiation that during the subsequent decade, which was to become so fertile scientifically, most notable contributions were made not only to technical development but also to our knowledge of the action of radiation on normal and pathologic tissues. The more penetrating roentgen rays could now reach any depth of the body, thus enabling careful biologic, physiopathologic and histopathologic observations. These contributions were further enhanced by similar observations made with the even more penetrating gamma rays of radium, which during this decade also began to find gradually increasing clinical applicability.

The first orthovoltage roentgen therapy unit at Harper Hospital was installed in 1921. Since, to cite Dr. James Case,[5] "We have not yet reached the stage of providing proper protection against the higher voltage tubes," a fact which earlier had led to such disastrous results with the lower voltage tubes, the preliminary efforts were directed to construction of devices for pro-

tection from both electrical and radiation hazards. Another disturbing element was the very low output of the original air-cooled tubes necessitating very long treatment times. Mr. Clifford Sherratt, electrical engineer and pioneer designer of high voltage radiation protection, honorary member of this Society, aided immeasurably in solving these contemporary problems so that at the beginning of 1922 routine clinical therapy was made possible.

The first unit had two air-cooled tubes which were housed in suspended self-contained lead drums and energized by a single transformer, enabling treatment of two patients simultaneously (Fig. 1, *A*, *B* and *C*). In the second unit the two tubes were housed in lead boxes and used for the treatment of the same patient through two opposite ports simultaneously; one box was placed beneath the treatment table and the other was suspended above it, with a flexible up and down movable arrangement (Fig. 2, *A* and *B*). For the third unit, a water-cooled tube with a much higher output which had become available was utilized and from this time on only one tube was energized by each transformer. The original lead drum was bisected and its upper half was replaced by a lead cubicle, which contained first the water-cooling and later the oil-cooling device of the tube (Fig. 3). One single patient was treated by each unit, the tube being fixed and the treatment table being moved up and down for the desired skin target distance. Orthovoltage units of this type were employed very successfully until recently when they were replaced by flexible shock-proof and radiation-proof apparatus provided with the del Regato mirror localizer and an aperture with a platform arrange-





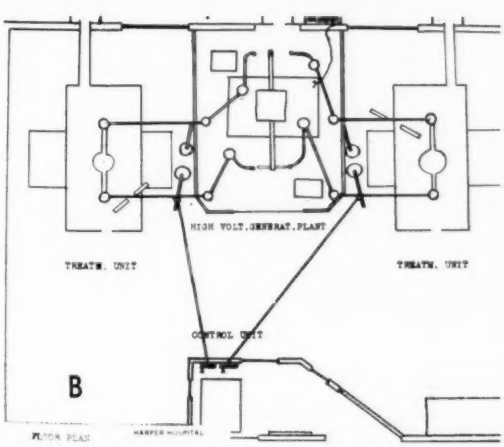


Fig. 1. First orthovoltage unit installed at Harper Hospital in 1921. (*A*) Photograph of the treatment room. A single transformer energized two air-cooled tubes which were housed in suspended self contained lead drums, enabling treatment of 2 patients simultaneously. (*B*) Floor plan showing the layout of the unit. (*C*) Diagram of the lead drum.

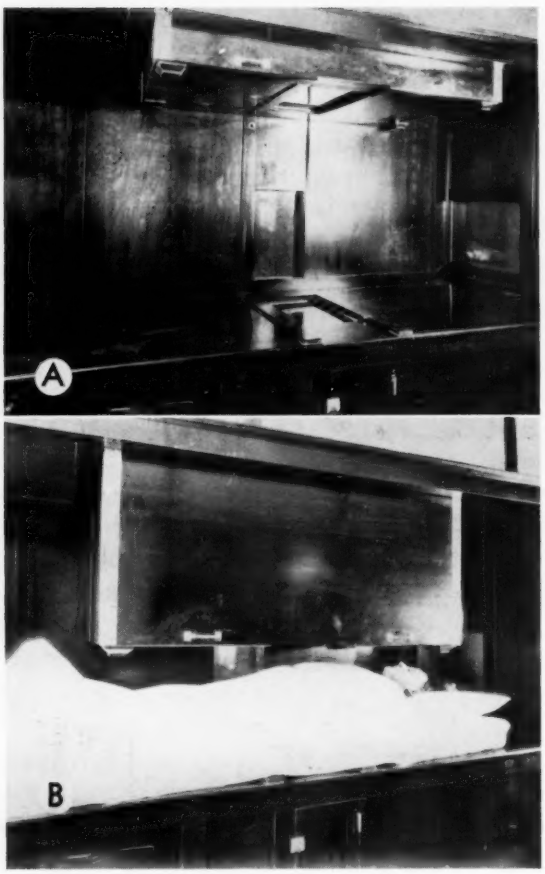


FIG. 2. Second orthovoltage unit. (*A* and *B*) The two air-cooled tubes were housed in individual lead boxes, one box being placed beneath the treatment table and the other suspended above it with a flexible up and down movable arrangement. This unit permitted treatment of a patient through two opposing ports simultaneously.

ment for geometric or anatomic outlining of the treatment fields.

As a result of promising experimental work by a few investigators at the threshold of the 1930's, a supervoltage roentgen therapy unit was added in 1931 and patients were treated by it starting in 1932. Briefly, the unit consisted of six 150 kv. constant potential cascaded transformers (Fig. 4) and a Lauritsen type unisectional tube with grounded anode.[21] This unit also underwent several modifications. Initially, two interchangeable heads were used, one of steel with a thin tungsten disk target and another of brass with a somewhat thicker gold disk target. During this period only one patient was treated at a time. Then a change was made to a "transparent" lead target (Fig. 5, *A*, *B* and *C*), the filament current was improved, and the controlling rod was insulated more firmly (Fig. 6). Since the transparent target was at a 45° angle, this permitted, with

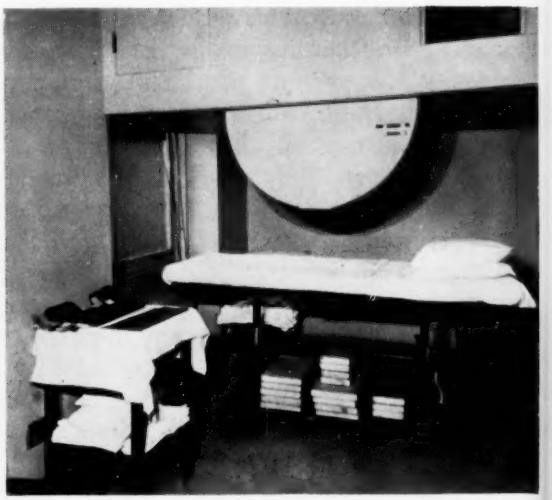


FIG. 3. Third orthovoltage unit. When a water-cooled tube with a much higher output became available, the lead drums of Figure 1 were bisected and their upper halves were replaced by lead cubicles which contained the water-cooling and later the oil-cooling system. The treatment table was moved up and down for the desired skin target distance, wooden blocks of various thicknesses being used for this purpose.

FIG. 4. First supervoltage unit installed at Harper Hospital in 1931. The energizing source consisted of six 150 kv. constant potential cascaded transformers.

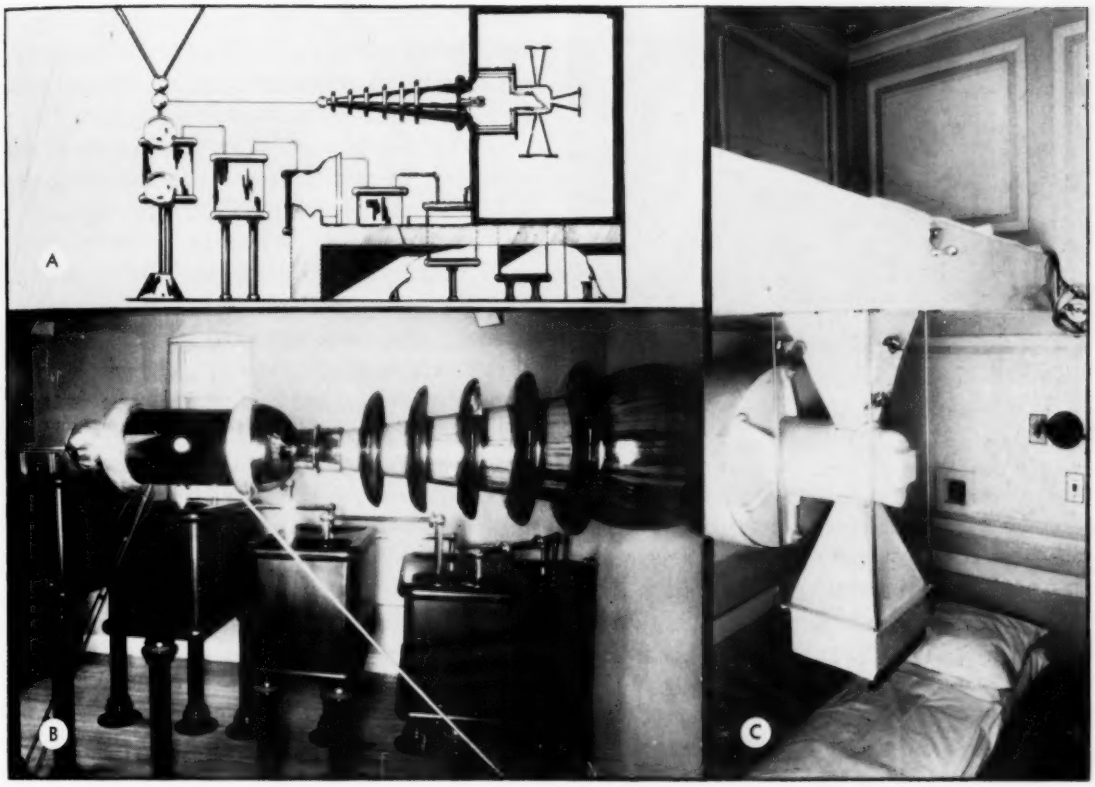


FIG. 5. Later improvement of the supervoltage unit. (*A*) Diagram of the unit. (*B*) Room of the generating plant containing the six constant potential cascaded transformers and the porcelain body of the Lauritsen type unisectional tube. (*C*) Lead-protected treatment room with a periscope window for observation and a loud speaker for communication. The transparent lead target of the anode grounded tube permitted treatment of 2 patients simultaneously. A third (axial) portal could be used at the same time for investigative purposes.

a slight filter correction, an equal output for two opposite fields. Thus 2 patients could be treated simultaneously, one in an upper berth with a fixed skin target distance and the other on a lower mobile table with a more flexible arrangement. Provision was also made for a third (axial) field which could be used at the same time for investigative purposes.

This unit was operated at 500–600 kv. constant potential, with 7 mm. Cu equivalent filtration, corresponding to a half value layer of 9 mm. Cu. The output was 20 r/min. at 50 cm. and the skin target distance of the mobile table could be varied between 50 and 70 cm. The protection which was designed by Mr. Sherratt was foolproof and the patients were observed during treatment by a built-in periscope. The unit was employed successfully for a quarter of a century. It was replaced four years ago by a 2 mev. Van de Graaff apparatus and the periscope for observing the patients was substituted by a closed circuit television system.

Of course, there are other types of apparatus, such as the betatron, the synchrotron, and the linear accelerator, and some teletherapy units with radioactive sources as Co^{60} and more recently Cs^{137} which notably augment the spheres of radiation therapy, but their consideration transcends the scope of our discussion this evening.

With the equipment available at Harper Hospital, an impressive number of diseases has been treated since the first orthovoltage unit was installed. The gyne-

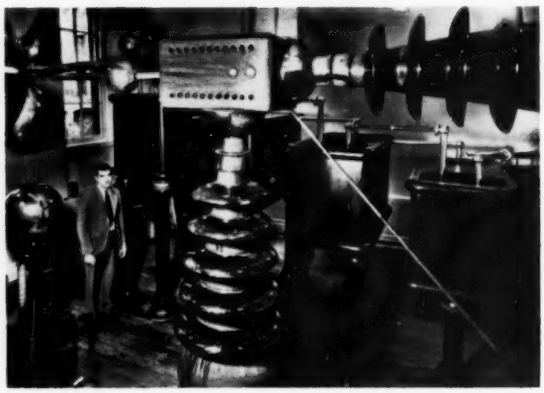


FIG. 6. Still later improvement of the supervoltage unit showing porcelain insulation of the filament supply generator.

cologic cancers represent a group in which radiation therapy, more than in any other group, was used extensively from the beginning. The series upon which this study is based includes 3,204 cases treated from 1922 to 1954, of which 592 cases were malignant neoplasms of the ovary, 2,059 cases were carcinoma of the cervix uteri and 553 cases were carcinoma of the endometrium. For a comparable evaluation of the results obtained with the various radiation modalities or their combinations with surgical methods, the five year survival rate is taken as the measuring yardstick and patients who could not be followed-up were assumed to have died from cancer. From 1922 to 1931 roentgen therapy was carried out with orthovoltage rays, from 1932 to 1936 half of the patients were treated by orthovoltage and the other half by supervoltage rays and since 1937 supervoltage rays have been used exclusively in all patients. An important change was also made as regards the general policy for radium application. Prior to 1928 the practice was to administer a dose which would produce little or no reaction on the surrounding normal structures, particularly those of the intestinal and urinary tracts. After 1928, the factitional reactions were considered to be unavoidable, and the radium dose was considerably increased. Commensurate with this, the orthovoltage roentgen dose was also increased and, finally, the full substitution of the supervoltage for the orthovoltage rays since 1937 led to a rather standardized and fairly uniform technique.

In malignant neoplasms of the ovary, the majority of which were carcinomas, the generally accepted method of combining surgery with external roentgen therapy was used throughout the series. Often alternation of surgery, consisting of removal of the primary neoplasm or of the larger recurrent or metastatic masses, and roentgen therapy was employed, particularly in tumors of lesser radiosensitivity.

The treatment of malignant neoplasms of the ovary is fraught with two great difficulties. First, the average case, because of absence or paucity of symptoms in the beginning, is diagnosed at a relatively late stage of disease after the dissemination has already taken place; secondly, the nature of the dissemination itself in the form of peritoneal implants or metastases to the regional lymph nodes is such that it entails special considerations in outlining the irradiation procedure. As is well known, the regional sphere of the ovary, even before the malignant neoplasm has broken through the ovarian capsule and produced peritoneal implants, is in the para-aortic area. The lymph channels originating in the ovary follow the course of the ovarian artery and lead to the upper lymph nodes of the para-aortic group. This means that in the majority of cases radiation therapy, to be effective, must include the upper abdomen in addition to the pelvis and lower abdomen. Since some irradiation of the kidneys cannot be avoided, the possible late effect produced on this organ must be weighed against the biologic longevity of the malignant neoplasm, which is a serious limiting factor. The presence of ascites, which accompanies dissemination both to the peritoneum and the high para-aortic lymph nodes in a high percentage of cases, is another serious limiting factor.

The problem of what program to follow is hard to solve. We generally made use of a plan according to which the more radio-

sensitive neoplasms received the largest doses possible in a relatively short time, whereas tumors of the adult type were irradiated with several less intensive fractionated courses over longer periods and were alternated with surgery. In not a few cases a prolongation of life beyond the five year period was obtained after as many as 3 to 4 operations followed by even more courses of radiation therapy.

The five year survivals in the 592 cases, arranged quinquennially, are given in Table 1. As may be seen, some improvement was obtained throughout the years, the over-all results rising from 18 to 31 per cent. However, the contribution of supervoltage radiation therapy which was used routinely after 1937 was rather disappointing. This series does not as yet reflect the effect of the use of instillation of various radioactive substances or chemical agents into the peritoneal cavity but it already appears that the over-all five year results will be little influenced with this new addition and that combined surgery and external radiation therapy will continue to remain the most acceptable method of treatment.

Unlike the malignant neoplasms of the ovary, carcinoma of the cervix uteri was the subject of most intense and controversial discussions for nearly half a century in respect to the type, extent and radicalism of the many procedures periodically recommended for its treatment. Of these, the various irradiation methods occupied a place no less conspicuous than the multitude of surgical techniques, and the appraisal of their relative merits became a difficult task. A review of a large series of cases with a heuristic glimpse into the salient chronologic phases of the evolution of treatment may aid in elucidating some aspects of the complex problem.

While caustic agents and various forms of cauterizations have been used for the treatment of carcinoma of the cervix uteri from time immemorial, its complete eradication has been attempted only since the development of surgery. The zenith of the surgical phase was reached during the second decade of the present century with the very radical Wertheim operation. It soon was realized, however, that, because of the great operative mortality, the high incidence of postoperative sequelae and the disappointing over-all five year survival results, a different approach to the problem was desirable. In 1915 radium therapy made its appearance and in the early 1920's it was complemented by orthovoltage roentgen therapy utilizing 200 kv. After another decade, and especially following the introduction of supervoltage roentgen therapy, irradiation with a combination of radium and roentgen rays became the predominant method, completely replacing surgery. At the height of this radiation phase, Dr. Kamperman,[15] Chief of the Department of Obstetrics and Gynecology at Harper Hospital, wrote in 1941, "There is now sufficient collected evidence to warrant the statement that the greatest of advances in the treatment of cervical carcinoma was made when the gynecologist relinquished the surgical treatment for radiation therapy."

Within a few years, however, notable contributions from Taussig,[30] Meigs,[23,24] Brunschwig[3,4] and others were published with the purpose of reviving and expanding the radical surgical procedures used either alone or in combination with various forms and sequences of radiation therapy. This aim stemmed mainly from three facts: first, in a certain number of cases radiation

TABLE I

MALIGNANT NEOPLASMS OF OVARY
FIVE YEAR SURVIVALS
1922–1954

Period	Cases/Survivals	Per Cent
1922–26	39/7	18
1927–31	60/11	18
1932–36	85/14	16
1937–41	82/20	24
1942–46	91/23	25
1947–51	128/34	27
1952–54	107/33	31

Total Cases Treated: 592.

therapy failed to bring about the desired results; secondly, the reactions which followed particularly the irradiation of the more resistant types of lesions were considered to be too severe; and thirdly, and most important of all, the tremendous development in the surgical techniques made possible the use of very extensive, commando type operations with complete safety to the patient. Although great emphasis was placed on the institutional investigative nature of these formidable procedures and the necessity of specially equipped teams to carry them out, the impact on the generally accepted treatment methods of the time could not be avoided, thus inaugurating the reintroduction of the surgical phase in the treatment of carcinoma of the cervix uteri.

The series of 2,059 cases of carcinoma of the cervix uteri treated at Harper Hospital from 1922 to 1954 by various methods reflects with fairly realistic fidelity the trends of the times. Of these, 1,958 were cases of carcinomas originating in the cervix of an intact uterus, and 101 were cases of primary carcinomas of the cervical stump in which a hysterectomy had been performed years previously for a benign condition. Radiation therapy, with intracavitary radium and external roentgen rays, was employed most frequently but a significant number of cases also had surgical procedures in various combinations. In the entire series the following four methods were used: (A) preoperative irradiation with external roentgen rays and intracavitary radium, followed within six to eight weeks by surgery and possible further irradiation; (B) radical surgery, followed by two to three courses, at eight to ten weeks from each other, of external roentgen therapy, complemented occasionally by intravaginal radium; (C) irradiation alone, consisting whenever possible of two courses of external roentgen therapy and intracavitary radium, at an interval of eight to ten weeks; and (D) irradiation alone in cases of recurrence after radical surgery.

The over-all five year survivals for the series, arranged quinquennially, are given in Table II which shows a continuous improvement in the results obtained. For the eight year period from 1947 to 1954, the over-all five year survival rate was practically 50 per cent.

For the purpose of studying the impact of the three aforementioned chronologic phases in the evolution of treatment, the 1,958 cases of carcinoma of the cervix uteri proper were arranged in five sexennial and one triennial period as follows: I. 1922–1927; II. 1928–1933; III. 1934–1939; IV. 1940–1945; V. 1946–1951; and VI. 1952–1954. The 101 cases of primary carcinoma of the cervical stump, which were treated by irradiation alone, will be considered separately.

As may be noted from Table III some patients already had been treated by a combination of preoperative irradiation and surgery (method A) during Period I; then the method was completely abandoned. It was revived during Periods V and VI. The five year survival rates ranged from 50 per cent during Period I to 70 per cent during Period VI, the average for Periods V and VI being 60 per cent. Only Stage I and II carcinomas were subjected to this type of combination, accounting for the increased survivals. Due, however, to the fact that they represented a small fraction of the total group, they had only a slight influence on the over-all results. A similar observation was made recently by Frick

TABLE II

CARCINOMA OF CERVIX UTERI
FIVE YEAR SURVIVALS
1922–1954

Period	Cases/Survivals	Per Cent
1922–26	236/36	15
1927–31	196/38	20
1932–36	267/81	30
1937–41	288/106	31
1942–46	420/187	40
1947–51	435/212	49
1952–54	217/115	50

Total Cases Treated: 2,059.

et al.[11] who state that "The application of radical surgical methods of treatment to primary surgical cancer has been associated with slight, but statistically not significant, improvement in the total cure rate." Rutledge and Fletcher,[29] who studied the effect of combination of megavoltage (22 mev.) irradiation and radical lymphadenectomy in Stage III carcinomas of the cervix, likewise express the opinion that "more intensive series and longer follow-up time will be necessary to determine whether there are changes in the salvage rate." Furthermore, there is already some evidence accumulating that, because of the usual postoperative sequelae which cannot be avoided and the marked increase in radiation fibrosis associated not infrequently with formation of lymphoceles, such combined treatment constitutes a radical procedure apt to be followed by an increased number of late complications. For these reasons one may affirm that, until full evaluation is obtained, the reintroduction of radical surgery following irradiation will continue to remain purely an investigative method.

The number of cases treated in our series by radical surgery and postoperative irradiation (method B) was practically the same throughout the six periods (Table III). As a rule, only the early cases were subjected

TABLE III

CARCINOMA OF CERVIX UTERI
FIVE YEAR SURVIVALS WITH
COMBINED METHOD
1922–1954

Period	A Cases/ Survivals	Per Cent	B Cases/ Survivals	Per Cent
I. 1922–27	10/5	50	22/8	36
II. 1928–33	0/0	0	17/11	60
III. 1934–39	0/0	0	21/10	50
IV. 1940–45	2/1	50	33/16	50
V. 1946–51	25/14	56	26/13	50
VI. 1952–54	10/7	70	14/8	58
Total Cases	47/27	57	133/66	50

A. Preoperative irradiation, surgery.
B. Surgery, postoperative irradiation.

TABLE IV

CARCINOMA OF CERVIX UTERI
FIVE YEAR SURVIVALS WITH IRRADIATION IN
RECURRENCES AFTER RADICAL SURGERY
1922–1954

Period	D Cases/Survivals	Per Cent
I. 1922–27	38/2	5
II. 1928–33	9/0	0
III. 1934–39	8/0	0
IV. 1940–45	4/0	0
V. 1946–51	9/2	22
VI. 1952–54	2/0	0
Total Cases	70/4	6

D. Surgery, recurrence, irradiation.

to this combination of treatment. The five year survival rate, excepting Period I, was 50 per cent or over. This contrasts sharply to the results obtained in recurrent cancers (method D) when the radiation therapy following radical surgery was prescribed only after the recurrent or metastatic lesions became manifest. As may be seen in Table IV, the largest number of such patients was treated during Period I when the surgical phase was still dominant. The results obtained were disastrous and continued to remain so during all subsequent periods in the greatly reduced number of cases in which it was used, the five year survival rate barely reaching 6 per cent.

In compiling the results obtained by irradiation alone (method C), the relative results were tabulated in addition to the absolute results for comparison (Table V). The former group includes all patients who received at least two full courses of irradiation eight to ten weeks apart, as has been the standard procedure in our institution since 1937. The latter group also comprises a certain number of patients who, for various reasons, received only one full course of irradiation, others in whom even one course could not be completed and all those patients who were treated for distant dissemination of the disease. Table V shows that, while the relative results obtained with the two course technique, excepting

TABLE V

CARCINOMA OF CERVIX UTERI
FIVE YEAR SURVIVALS WITH
IRRADIATION ALONE

Period	Absolute		Relative	
	Cases/ Survivals	Per Cent	Cases/ Survivals	Per Cent
I. 1922–27	197/26	12	—	—
II. 1928–33	214/46	21	—	—
III. 1934–39	304/99	33	103/45	44
IV. 1940–45	412/175	42	315/157	50
V. 1946–51	413/195	47	340/171	50
VI. 1951–54	168/85	51	131/71	54

Total Cases Treated: 1,708.
The relative group includes only cases which had 2 full (or several partial) courses of irradiation, eight to ten weeks apart.

the first few years, remained practically the same, the absolute results rose steadily and during Period VI approximated the relative results. This table also shows that comparatively more patients were treated to the full extent from period to period, thus indicating a more favorable stage of the disease at the initiation of the irradiation.

Analysis of the ratios of the cases treated by the three combined methods (A, B, and D) to each other and to the cases treated by irradiation alone (C) permits the following deductions (Table VI):

TABLE VI

CARCINOMA OF CERVIX UTERI
RATIO OF COMBINED METHOD CASES TO
IRRADIATION CASES
1922–1954

Period	Ratio			
	A	B	C	D
I. 1922–27	5.0:	10.1:	100:	19.3
II. 1928–33	0.0:	7.9:	100:	4.2
III. 1934–39	0.0:	6.9:	100:	2.6
IV. 1940–45	0.5:	8.0:	100:	1.0
V. 1946–51	6.1:	6.3:	100:	2.2
VI. 1952–54	5.8:	8.2:	100:	1.2

A. Preoperative irradiation, surgery.
B. Surgery, postoperative irradiation.
C. Irradiation alone.
D. Surgery, recurrence, irradiation.

(1) Preoperative irradiation followed by radical surgery (method A), which was used to some extent initially, has been replaced by irradiation alone (method C); the combination was reintroduced in the mid-1940's but its scope is being restricted to more and more rigidly selected cases. The sexennial ratio to the cases treated by irradiation alone was 5.0:100 in Period I, then it dropped to 0 and rose to 6.1:100 in Period V and 5.8:100 in Period VI.

(2) Radical surgery followed by postoperative irradiation (method B) continued to be used in approximately the same proportion, particularly in the early cases. The sexennial ratios ranged from 6.3:100 in Period V to 10.1:100 in Period I.

(3) Irradiation of recurrent carcinomas following radical surgery (method D) persistently yielded extremely poor results and therefore is now used very rarely. The high sexennial ratio of 19.3:100 in Period I gradually dropped to a low of 1.2:100 in Period VI.

It may, therefore, be stated that in the treatment of carcinomas of the cervix uteri irradiation constitutes the major method. The optimal results are obtained by a comprehensive combination of intracavitary radium or other radioactive substances and external irradiation with roentgen or gamma rays. As reflected in this extensive series, all improvements in the over-all five year results throughout the years have been contributed chiefly by some important advance in technologic development or by a more judicious selection of the modalities used for irradiation. The effect of reintroduction of radical surgery upon the over-all results appears to be statistically small and needs further investigative evaluation.

In studying the 101 cases of primary carcinomas of the cervical stump in which a hysterectomy was performed years previously for some benign condition, two interesting observations were made. (1) The introduction of an intravaginal radium technique protracted over seven days, as a complement to the external supervoltage roentgen therapy, more than doubled the

survival results obtained. As shown in Table VII, whereas during the first three sexennial periods the five year survivals averaged 22 per cent, since 1940 they have risen to between 54 and 59 per cent for the three subsequent periods. (2) However, even more interesting and greatly surprising is the fact that, as shown in Table VIII, the ratio of incidence of primary carcinoma of the cervical stump to that of carcinoma of the cervix of an intact uterus rose from 2.6:100 during Period I to 12.3:100 during Period VI, or more than a five-fold increase. The patients in this group were referred for radiation therapy, which was used as the sole method, on an average thirteen years after hysterectomy, the range extending from one year to fifty years. The increase in the ratio started after World War II and was marked during Periods V and VI. Apart from perhaps an effect of changing population in an industrial area, no explanation is available for this phenomenon. As far as could be determined not one of these patients had previous radiation therapy in any form for the benign condition for which the hysterectomy was performed.

The heuristic approach assumes even a greater significance in the appraisal of the optimal method of treatment in carcinoma of the endometrium, encompassing the lesions of the corpus and fundus uteri. The medical literature contains numerous notable publications dealing with the use of various techniques of radiation therapy and their possible combinations with surgical procedures to achieve the highest statistical yield in the results obtained. In some of these publications preoperative irradiation, either in the form of intracavitary radium application alone or in association with external radiation therapy, is recommended; in others irradiation, usually in the form of external radiation therapy, is prescribed postoperatively; and still in others surgery alone is used and irradiation is reserved for those instances in which recurrence or dissemination has occurred. There is general agreement on the fact that irradiation, as the sole method of treatment, should be undertaken only in the inoperable cases, mostly for the purpose of palliation.

In our series of 553 cases of carcinoma of the endometrium treated from 1924 to 1954 by radiation therapy and surgery in various combinations, three methods were used: (A) preoperative irradiation with intracavitary radium and external roentgen rays, hysterectomy six to eight weeks later, and postoperative irradiation with external roentgen rays two to three weeks after the operation; (B) hysterectomy and 2 or 3 courses of postoperative irradiation with external roentgen rays, associated very rarely with intravaginal radium, at intervals of eight to ten weeks from each

TABLE VII

CARCINOMA OF CERVICAL STUMP
FIVE YEAR SURVIVALS WITH IRRADIATION
1922–1954

Period	Cases/ Survivals	Per Cent
I. 1922–27	7/0	0
II. 1928–33	4/1	25
III. 1934–39	7/3	29
IV. 1940–45	17/10	59
V. 1946–51	43/23	54
VI. 1952–54	23/13	56
Total Cases Treated:	101	

TABLE VIII

RATIO OF CARCINOMA OF CERVICAL STUMP TO CARCINOMA OF CERVIX
1922–1954

Period	Cervical Stump Cases	Cervix Cases	Ratio
I. 1922–27	7	267	2.6:100
II. 1928–33	4	240	1.6:100
III. 1934–39	7	333	2.1:100
IV. 1940–45	17	451	3.8:100
V. 1946–51	43	473	9.1:100
VI. 1952–54	23	194	12.3:100
Total Cases:	101	1,958	

other; and (C) irradiation alone in the inoperable cases.

The physical factors of the irradiation, as in carcinoma of the cervix, conformed to the technical improvements of the time. Until 1924, when radiation therapy of carcinoma of the endometrium was started at Harper Hospital, surgery constituted the sole method of treatment. Radium was used occasionally on a trial and error basis, mostly in the inoperable and recurrent cases. The favorable impression gained in conjunction with carcinoma of the cervix, where deep roentgen therapy was started two years earlier, soon led to a fundamental change in this situation. First, the inoperable cases of carcinoma of the endometrium were subjected to combined radium and roentgen therapy, then the operable cases, in which hysterectomy was performed, were irradiated postoperatively with roentgen rays. Initially, here too as in carcinoma of the cervix, the dosage with both agents was rather low so as to avoid any distressing side reaction. After a few years, however, the fallacy of such a policy became evident and the dosage was raised considerably.

In 1928, Dr. Kamperman[15,16] conceived the plan of preoperative irradiation in carcinoma of the endometrium, consisting of a full course of intracavitary radium and external roentgen therapy. By placing radium within the uterine cavity, it is possible to achieve a more thorough irradiation of the entire pelvis than is the case with postoperative roentgen therapy alone, after the uterus has been removed. There are two other reasons why such a procedure appears more advantageous. First, it provides a technique for performance of dilatation and curettage and insertion of intrauterine radium at the same time. If the microscopic examination of the curettings indicates the presence of a functional or polypoid endometrium, the radium dose is adjusted to produce exovulation, without supplemental roentgen therapy. However, if the report is that of a carcinoma, the radium application is prolonged and is followed by a full course of roentgen therapy which, then, constitutes the preliminary irradiation. Experience over the years shows that, since carcinoma of the endometrium is for the most part a postmenopausal occurrence with fresh, often dramatic, hemorrhage as its most common symptom, such a procedure leads to a somewhat earlier diagnosis in the average case. Secondly, as confirmed by the experiments of Altemeier and Jones,[1] the preliminary irradiation of the pelvis reduces the hazards of infection, almost completely eliminating operative mortality.

The preliminary irradiation is followed within six to eight weeks, depending on the reaction produced, by surgery. The operative procedures varied to some extent in our series, but in the majority of cases a total hysterectomy with bilateral oophorectomy, as recommended by Kamperman, was performed.

A second course of irradiation, consisting of roentgen therapy alone, is administered within two to three weeks after the hysterectomy.

This method has been used in Harper Hospital cases continuously since its introduction in 1928. The only modifications were made in 1933 when, for four years, half of the cases were treated with supervoltage roentgen therapy for comparison, and in 1937 when orthovoltage roentgen therapy was completely replaced by supervoltage roentgen therapy.

During the same time a significant number of patients, who had had hysterectomy first and in whom roentgen therapy was advised postoperatively, was accepted for irradiation from other institutions. The majority of these patients received the maximum allowable radiation dose but, excepting a few instances, without the benefit of intracavitary radium. This circumstance permits a good comparison of the two methods.

In the inoperable cases irradiation alone was used, consisting of two courses of external roentgen therapy and intracavitary radium at an interval of eight to ten weeks, whenever possible.

The over-all five year survivals arranged

TABLE IX

CARCINOMA OF ENDOMETRIUM
FIVE YEAR SURVIVALS
1924–1954

Period	Cases/Survivals	Per Cent
1924–26	12/4	33
1927–31	29/13	45
1932–36	49/25	47
1937–41	83/46	55
1942–46	92/58	63
1947–51	189/113	60
1952–54	99/63	64
Total Cases Treated:	553	

quinquennially are shown in Table IX. As may be noted, there was a steady and definite improvement in the results. Since 1937, when the present procedures had become fairly well standardized, the quinquennial survival rates have increased from 55 to 64 per cent. Despite the fall to 60 per cent during the period of 1947 to 1951, this represents a notable progress which, as we shall see, may be explained by studying the change in combination of the methods used.

Based on the aforementioned historic evolution, the series of 553 cases of carcinoma of the endometrium may be divided into those treated before and those treated after 1937. However, to gain a better insight into the constancy of the results, the latter cases are again divided into those of the first ten years after 1937 and those of the next eight years. Thus we may distinguish three periods: I. 1924–1936; II. 1937–1946; and III. 1947–1954. As may be seen from Table X the five year survival rates of the patients treated according to method A amounted to 80 per cent during Period I and II and to 78 per cent during Period III. The corresponding rates for the patients treated with method B were 50 per cent for Period I and II and 55 per cent for Period III. The cases treated by irradiation alone (method C) yielded a five year survival rate of 35 per cent during Period I, 40 per cent during Period II and 35 per cent during Period III. The over-all results for all cases were 47 per cent during Period I, 60 per cent during Period II and 61 per cent during Period III.

Three deductions may be made from a comparative analysis of these results.

1. The marked superiority of method A over method B has continued to be evident throughout the three periods.

2. This continued superiority of method A has altered the aspect of the entire series in two ways: (a) it has increased the ratio of the operable cases to the inoperable cases from 11:10 during Period I to 14:10 during Period II and 30:10 during Period III (Table XI), representing a three-fold increase. However, even more significant is the

TABLE X

CARCINOMA OF ENDOMETRIUM
FIVE YEAR SURVIVALS RELATED TO METHOD OF TREATMENT
1924–1954

Period	A		B		A and B Cases Combined		C		A, B and C Cases Combined	
	Cases/ Survivals	Per Cent	Cases/ Survivals	Per Cent	Cases/ Survivals	Per Cent	Cases/ Survivals	Per Cent	Cases/ Survivals	Per Cent
I. 1924–36*	10/8	80	37/19	50	47/27	58	43/15	35	90/42	47
II. 1937–46	64/52	80	39/19	50	103/71	70	72/33	40	175/104	60
III. 1947–54	143/101	78	73/40	55	216/151	70	72/25	35	288/176	61

Total Cases Treated: 553.
A. Preoperative irradiation, hysterectomy, postoperative irradiation.
B. Hysterectomy, postoperative irradiation.
C. Irradiation alone in inoperable cases.
* Method A was started in 1928.

TABLE XI

CARCINOMA OF ENDOMETRIUM
RATIO OF OPERABLE CASES TO
INOPERABLE CASES
1924–1954

Period	Operable Cases A and B	Inoperable Cases C	Ratio
I. 1924–36*	47	43	11:10
II. 1937–46	103	72	14:10
III. 1947–54	216	72	30:10

* Method A was started in 1928.

fact that (b) within the operable group itself it has raised the ratio of preirradiated operable cases (method A) to the postirradiated operable cases (method B) from 3:10 during Period I to 16:10 during Period II and 20:10 during Period III (Table XII), or nearly a seven-fold increase.

3. The increase in the number of the cases operated upon was accompanied by a corresponding decrease in the number of cases which remained to be treated by irradiation alone. Thus the ratio of the preirradiated inoperable cases (method A) to the inoperable cases (method C) was 2:10 during Period I, 9:10 during Period II and 20:10 during Period III (Table XIII). In the two periods after 1937 when both method A and method C had become fairly well standardized the decrease was slightly

TABLE XII

CARCINOMA OF ENDOMETRIUM
RATIO OF PREIRRADIATED OPERABLE CASES TO
POSTIRRADIATED OPERABLE CASES
1924–1954

Period	Pre-irradiated Operable Cases A	Post-irradiated Operable Cases B	Ratio
I. 1924–36*	10	37	3:10
II. 1937–46	64	39	16:10
III. 1947–54	143	73	20:10

* Method A was started in 1928.

TABLE XIII

CARCINOMA OF ENDOMETRIUM
RATIO OF PREIRRADIATED OPERABLE CASES TO
INOPERABLE CASES
1924–1954

Period	Pre-irradiated Operable Cases A	Inoperable Cases C	Ratio
I. 1924–36*	10	43	2:10
II. 1937–46	64	72	9:10
III. 1947–54	143	72	20:10

* Method A was started in 1928.

over two-fold. In other words, more than twice as many patients were subjected to method A treatment during Period III than during Period II. This had two effects on the over-all results of the series during these periods: (a) it reduced the survival rate for method A from 80 per cent during Period II to 78 per cent during Period III and (b) it also reduced the survival rate for method C from 40 per cent during Period II to 35 per cent during Period III. Due to the fact that the favorable effect of preliminary irradiation helped to extend the criteria of operability, more of the questionable borderline cases have been transferred to group A, leaving only the more severe cases in group C. Although this less rigid selection of cases produced slight lowering of the five year survival rates for both groups individually, the two-fold increase in the ratio of cases subjected to method A, with its superior results during Period III, has raised the over-all results to 61 per cent as compared to 60 per cent during Period II.

It may, therefore, be stated that in the treatment of carcinoma of the endometrium a combination of surgery and irradiation plays a major role. The optimal results are obtained by a method consisting of preoperative irradiation with intracavitary radium or equivalent radioactive substances and external roentgen or gamma rays,

followed within six to eight weeks by total hysterectomy and bilateral oophorectomy, and supplemented, when necessary, with a second course of external radiation therapy. Irradiation alone is used only in the cases adjudged inoperable primarily or following completion of the preliminary irradiation when surgery still remains contraindicated.

Of course, in viewing the problem of treatment of gynecologic cancers in a broader perspective, there are other factors of greater importance which must be considered. Among these are the natural history of the cancer, its histopathologic structure, the mode of its local and metastatic spread, and, foremost, its biologic behavior with respect to anatomic site, whether located in a silent area as malignant neoplasms of the ovary, in an area of insidious onset as cancer of the cervix or in a dramatically symptomatic area as cancer of the endometrium. The over-all five year survivals of 31 per cent, 50 per cent, and 61 per cent in the three respective areas amply reflect this inescapable conclusion. The immense contribution of radiation therapy in helping to bring about these results, however, cannot be denied. Thus, the almost insurmountable task of the early pioneers, of whom so many became heroic martyrs, in establishing the clinical merit of radiation therapy has been "wonderfully" fulfilled.

My great teacher, Preston M. Hickey,[13] who in his Caldwell Lecture of 1928 artfully epitomized the life history of Eugene Caldwell and who skillfully reviewed all his important contributions to radiology, concluded his lecture by saying: "The speaker's task will not have been in vain if you who make up this assembly are strengthened and encouraged by the glimpses which we have had of one who so nobly exemplified the ideals of our specialty." It is my ardent hope that you who make up this distinguished assembly this evening are equally strengthened and encouraged by the "heuristic" glimpses which we have had of the slow rhythmic evolution of radiation therapy, particularly in reference to the treatment of gynecologic cancers. To paraphrase the words of the ancient philosopher, "To know the truth is not as important as to love the truth."

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DEMONSTRATION OF LYMPH NODE METASTASES BY PELVIC VENOGRAPHY*

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PROGNOSIS in carcinoma of the cervix is in great part dependent upon the presence or absence of pelvic lymph node involvement.[1] While radioresistance of the neoplasm may be a possibility, certainly it has not been uncommon in patients dying of cancer of the cervix to find the treated primary lesion under control but considerable residual disease in the pelvis. In a collected series of cases[7] treated by surgery, a 61 per cent five year survival was reported when the pelvic lymph nodes were normal as compared to a 21 per cent five year survival if these nodes were involved by metastatic cancer. The incidence of positive pelvic lymph nodes as reported by Graham and Graham[6] is 15 per cent for LON† I, 27 per cent for LON II, and 66 per cent for LON III. This high incidence makes control of the lymphatic dispersions a critical problem in the treatment of cancer of the cervix.

There can be no doubt that irradiation can destroy tumor in the pelvic lymph nodes, although the frequency with which this occurs and the necessary dosage range is not known.[3,14,16] Kottmeier[10] has presented patients with positive pelvic lymph nodes who, on re-exploration years after radiation therapy, failed to show evidence of tumor. In a series[15] of patients staged as LON III who were treated with the betatron to a minimum of 6,000 r whole pelvis irradiation with subsequent lymphadenectomy, the incidence of histologically positive lymph nodes was well below the expected incidence of unirradiated cases.

Because of the inability to predetermine involvement of the lymph nodes, present techniques of radiation therapy include the usual lymph node sites within the treatment field. This needlessly results in extensive and potentially hazardous irradiation for those many patients whose lymph nodes are not involved. If the presence of these metastatic lymph nodes were known, more vigorous treatment would be justified and the cases without lymph node involvement could be spared this irradiation safely.

Lymph node involvement has been shown to be equally significant in cases of persistent disease. In a series of patients where exenteration was performed for persistent cancer, Bricker and Butcher[4] found only 2 out of 19 patients with positive lymph nodes who survived for three years. This is contrasted to a survival of 25 out of 56 patients when the lymph nodes were negative. Furthermore, the recognition of involved para-aortic lymph nodes would eliminate needless laparotomies, since such involvement makes these patients incurable.

The main groups of lymph nodes affected by metastatic carcinoma from the cervix lie along the vascular channels of the pelvis.[14] The venous channels, being thin-walled and of low intraluminal pressure, are easily distorted by enlarged and firm lymph nodes. This finding has been confirmed by several authors.[2,7]

TECHNIQUE

The veins of the pelvis can be opacified by several methods. The injection of a contrast medium into the marrow of the pelvic bones and the trochanteric region of the femur has been used.[7,11] The findings by this method are somewhat indirect and the opacification of the veins probably is less optimal than by a more direct route. This method is also subject to a low but definite incidence of pulmonary emboli, osteomyelitis and other complications.[12] Injection of

† LON = League of Nations staging.

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the contrast medium into the dorsal vein of the clitoris[7] and interstitial injection into the uterus also have been used to opacify the pelvic veins. We have selected the direct approach advocated by several authors.[2,5,8,9]

The technique is quite simple. It consists of bilateral percutaneous puncture of the femoral veins and passage of polyethylene catheters into the external iliac veins over metal guide wires. The tip of the catheter lies approximately 10 cm. distal to the junction of the internal and external iliac veins. Twenty-five cc. of 25 per cent hypaque is injected simultaneously into both catheters as quickly as possible and roentgenograms are obtained using a rapid film changing device.

The examination is carried out in two stages: the first without compression of the inferior vena cava, and the second with compression by a plastic balloon.

Roentgenography is done with the patient in the supine position, although occasionally additional oblique projections are utilized. With this technique, excellent opacification of the major vessels is obtained. The veins are fully distended by the large bolus of the medium and the opacification is nearly optimal with this direct approach. At the completion of the examination, excretory pyelograms are made sparing the patient an additional injection of contrast medium.

We have had no significant complications in our series of 31 cases. Helander and Lindbom[8] reported only 1 case with a serious complication. This consisted of pulmonary infarcts and emboli following a thrombus in the femoral and iliac veins. Early in our study, the tip of the guide wire broke off in the soft tissues in 2 patients. This was due to faulty manufacture of the wire and, since correction of this defect, no further complications have occurred.

NORMAL FINDINGS

Without compression of the inferior vena cava (Fig. 1), the external and common iliac veins and the inferior vena cava, as well as any abnormal filling of the venous channels, are well seen. With compression (Fig. 2), there is retrograde filling of the internal iliac vein down to the level of a competent valve. While somewhat variable, this distance is approximately 5 cm. from the junction of the internal and external iliac veins. Usually the obturator vein does not fill.

Several normal variations may occur within the veins of the pelvis. These have been pointed out by Helander and Lindbom[8] and by Bartley,[2] who have studied these veins both in operative cases and in the postmortem status when they are in a fixed, expanded state. While usually there is a single internal iliac vein on both sides, at times there may be two vessels (internal and middle iliac) on one or both sides of the pelvis. Occasionally, an internal iliac vein enters the common iliac vein in the region of the promontory. Normally, the iliac artery and aorta, as they cross the left common iliac vein, may indent and compress it. Indentations may also appear at the junction of the external and internal iliac veins due either to compression by the internal iliac artery or to "jet" dilution if no reflux occurs. While reflux into the internal iliac veins usually occurs down to a symmetric level, occasionally the competent valve is located higher on one side than the other. Reflux into the internal iliac veins may occur without compression, although in Bartley's[2] experience this was either bilateral or not at all. Filling of one or both ascending lumbar veins occurs without compression.

PATHOLOGIC FINDINGS

The presence of a firm tumor mass adjacent to the thin-walled, low-pressure vein may make itself apparent in several ways:

(1) *Indentation of the vein* (Fig. 3, 4, 5 and 7). This must be differentiated from the normal indentations. Abnormal indentations usually occur about the junction of the internal and external iliac veins and along the posterior and lateral margins of the common iliac veins, where normal indentations do not occur.

(2) *Nonfilling of a part of the vein because*

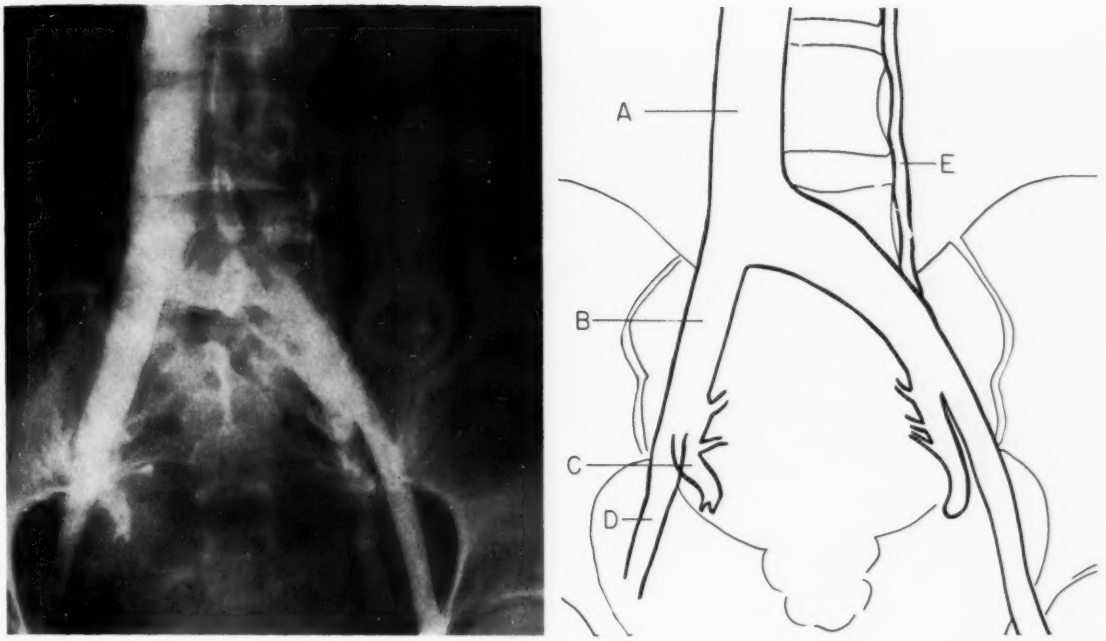


Fig. 1.

Normal pelvic venogram without compression. On the diagram, *A*—inferior vena cava, *B*—right common iliac vein, *C*—hypogastric vein, *D*—external iliac vein, *E*—ascending lumbar veins. Reflux into the internal iliac veins can occur normally without compression, as can filling of either or both ascending lumbar veins.

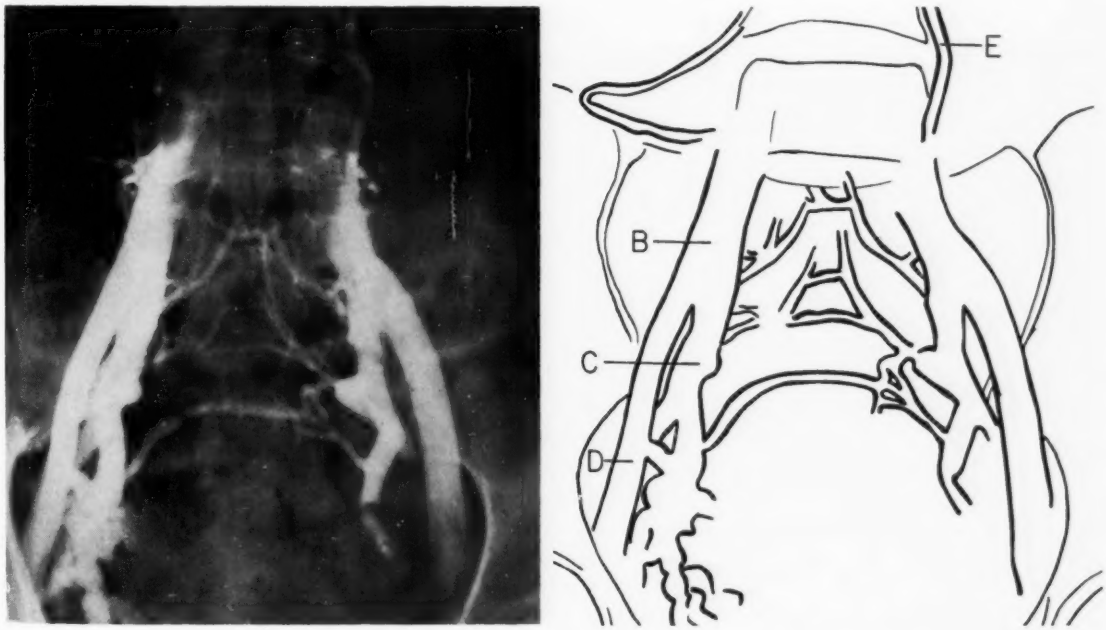
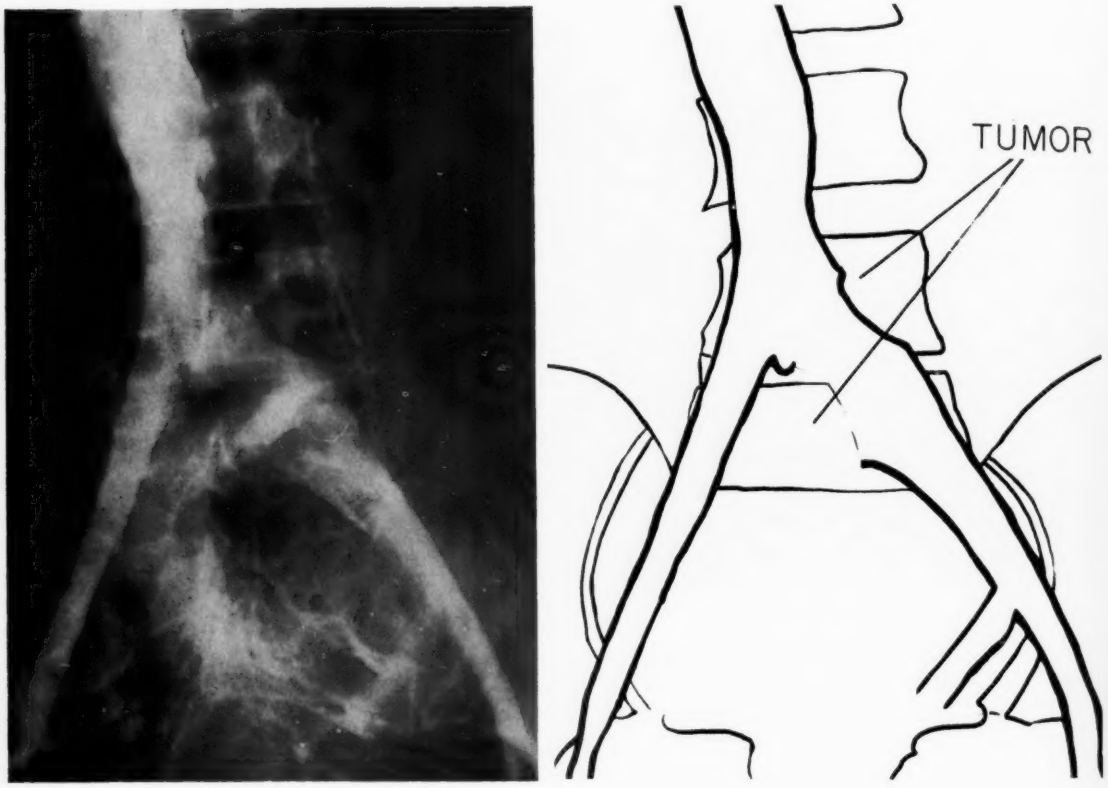


Fig. 2.

Normal pelvic venogram with compression. On the diagram, *B*—right common iliac vein, *C*—hypogastric vein, *D*—external vein, *E*—ascending lumbar veins. Asymmetric reflux with a "varicocele" on the right and a well-defined competent valve on the left is demonstrated.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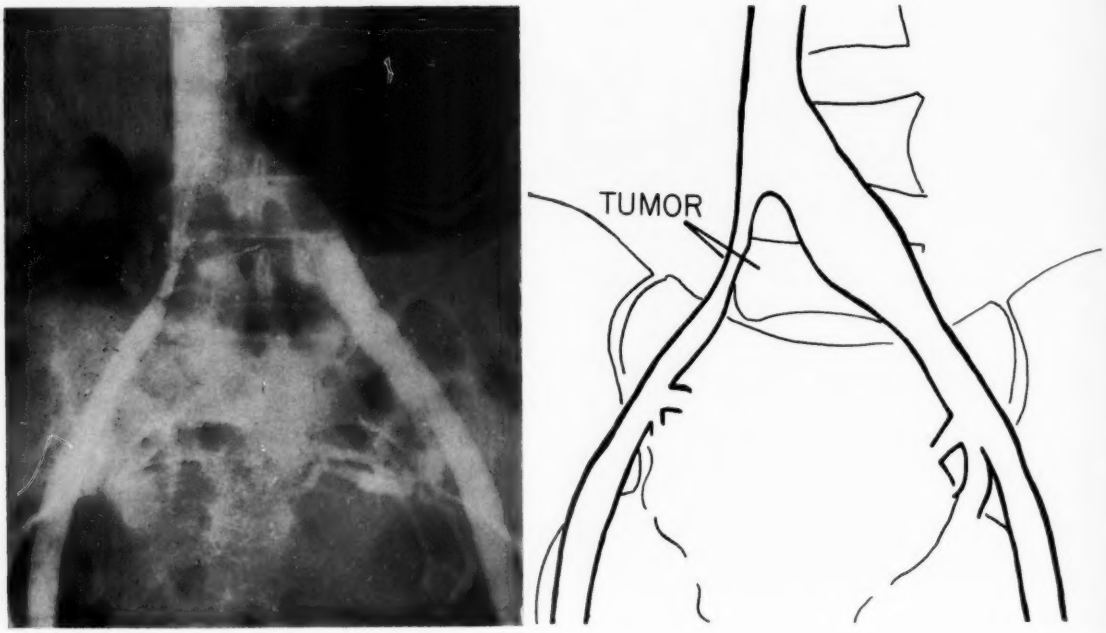

TUMOR

Fig. 3.

This fifty year old patient was diagnosed as having carcinoma of the cervix, LON III and she received radium and parametrial Au^{198} therapy. Microscopic examination of the lymph nodes after extraperitoneal lymphadenectomy did not show metastatic cancer. Six months later the patient returned with bilateral parametrial masses. There was no pain or leg edema.

A venogram made without compression demonstrates scalloped defects surrounding the left common iliac vein and the adjacent vena cava.

At operation a large tumor mass was found about the lower vena cava and left common iliac vein. Biopsy revealed metastatic epidermoid carcinoma.

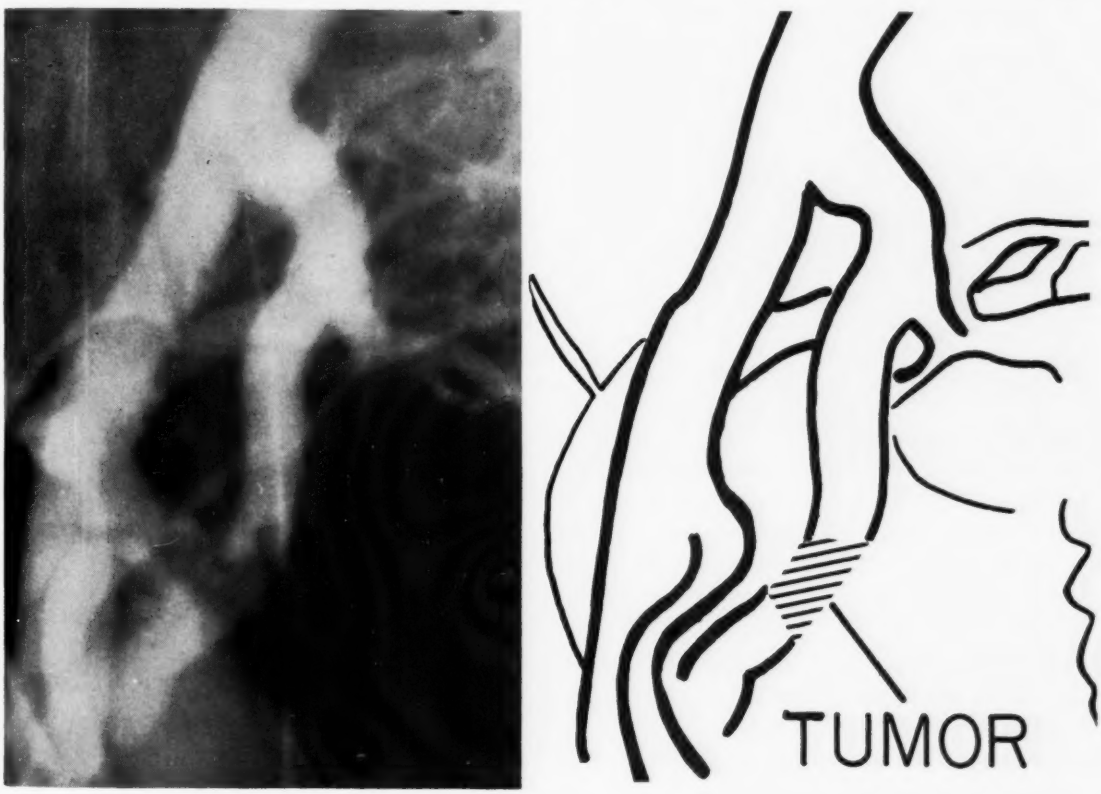


Fig. 5.

Venogram of a patient with a diagnosis of carcinoma of the cervix, LON III, which shows distortion and a pressure defect of the right hypogastric vein.

This patient received radium and parametrial Au^{198} therapy. At lymphadenectomy, a 2.5 cm. lymph node was found adjacent to the hypogastric vein 5 cm. proximal to its junction with the external iliac vein. Microscopic examination showed metastatic epidermoid carcinoma.

Fig. 4.

In 1950 this thirty-three year old female was treated with radium and roentgen therapy (dosage unknown) for carcinoma of the cervix. Nine years later a mass was palpated at the brim of the pelvis, on the right side. There was no leg pain or edema.

Circumferential narrowing of the right common iliac vein immediately caudal to the vena cava is seen on the venogram.

At laparotomy a 1 cm. lymph node was found between the iliac artery and ureter. Microscopic section of this mass revealed metastatic epidermoid carcinoma.

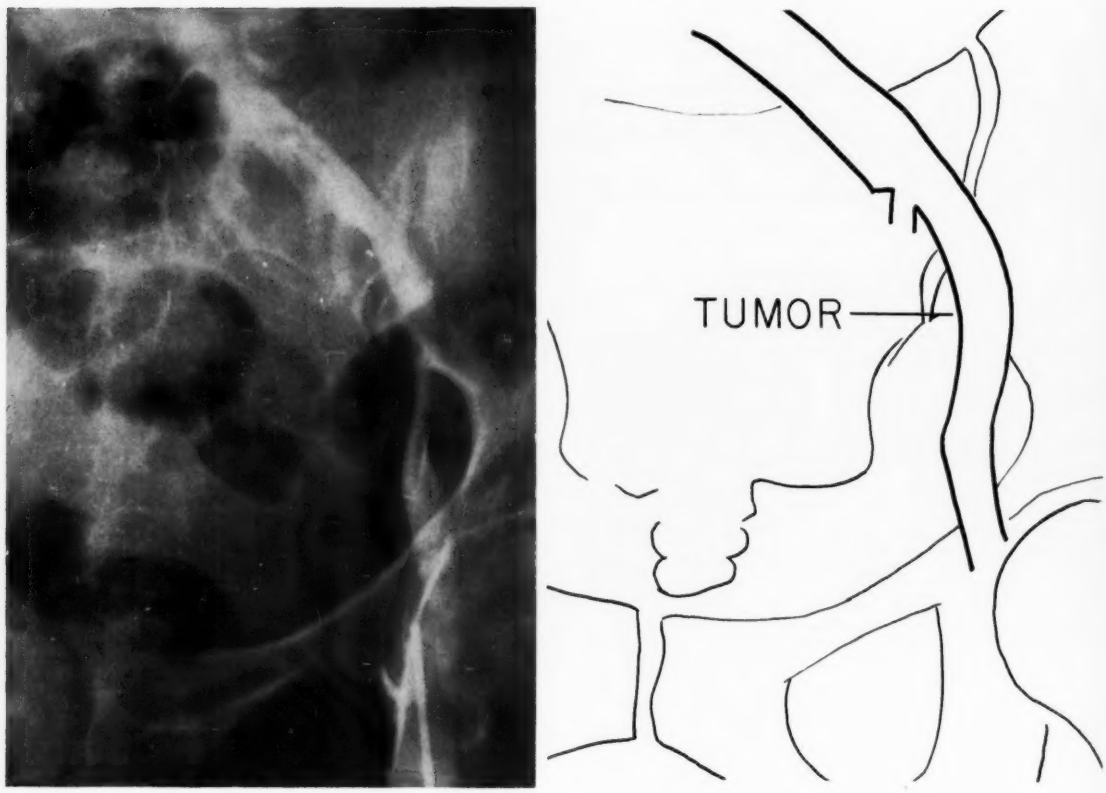


FIG. 6.

Venogram of a fifty-six year old female with carcinoma of the cervix, LON III, demonstrates displacement of the left external iliac vein with lateral bowing. There is no reflux into the left hypogastric vein.

The patient was treated with radium and parametrial Au^{198}. At the time of extraperitoneal lymphadenectomy, firm lymph nodes, 2 cm. in diameter, which were positive for epidermoid carcinoma, lay at the bifurcation of the common iliac vein.

of deficiency of flow in the normal direction or failure of retrograde filling (Fig. 6, 7 and 8). Thrombosis and periphlebitis may cause nonfilling of a part of the vein but it is uncommon and is not associated with other venographic manifestations of a mass lesion. The absence of reflux into one internal iliac vein when it is present on the opposite side, or marked asymmetry of the reflux level without demonstration of a valve and without evidence of a thrombus, is a definite sign of tumor.

(3) *Displacement of a vein* (Fig. 6). In Helander and Lindbom's[8] series displacement was quite uncommon, although it is certainly difficult to estimate.

(4) *Contrast filling of abnormal anastomoses* (Fig. 8). Without findings of the three changes listed above, abnormal anastomoses are only suggestive of venous obstruction by metastatic nodal compression.

RESULTS

It has been the practice in this hospital to perform an extraperitoneal lymphadenec-

»»→

FIG. 8.

Six months following radium and parametrial Au^{198} therapy for carcinoma of the cervix, LON III, this patient developed obstruction of the left ureter. A nephrectomy was done and the pelvis was found to be free of tumor. One year after the initial therapy she developed left hip pain and a palpable left pelvic mass.

This venogram shows an extreme example of collateral circulation that developed following tumor obstruction of the iliac veins. The veins outline a huge pelvic and lower abdominal mass. The patient was explored and a large necrotic epidermoid carcinoma was found surrounding the vessels.

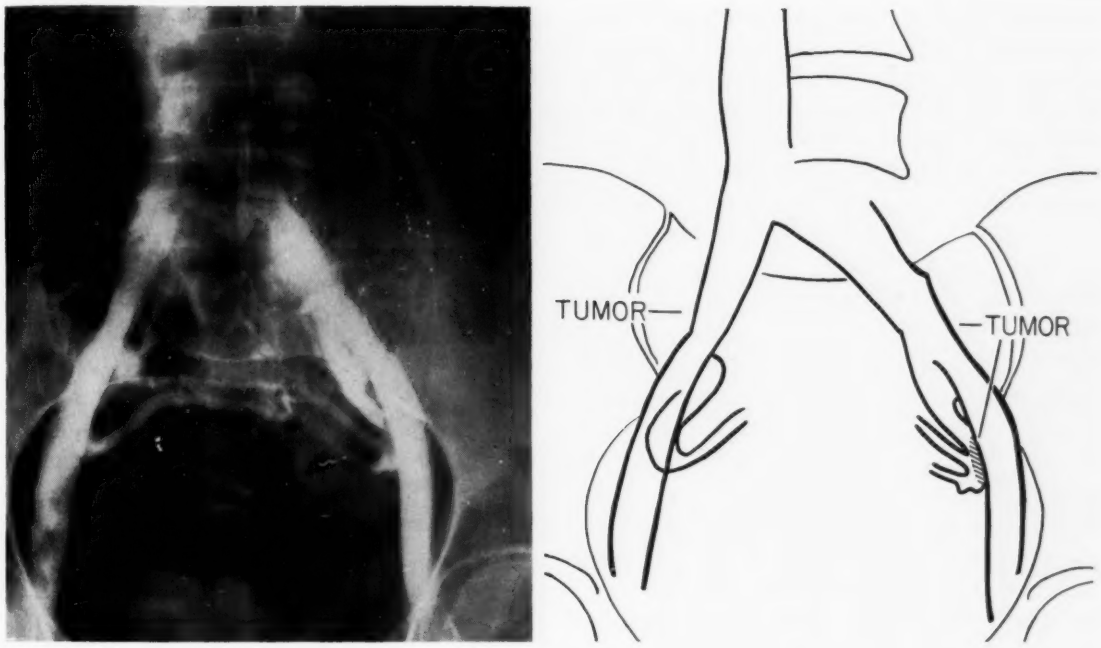
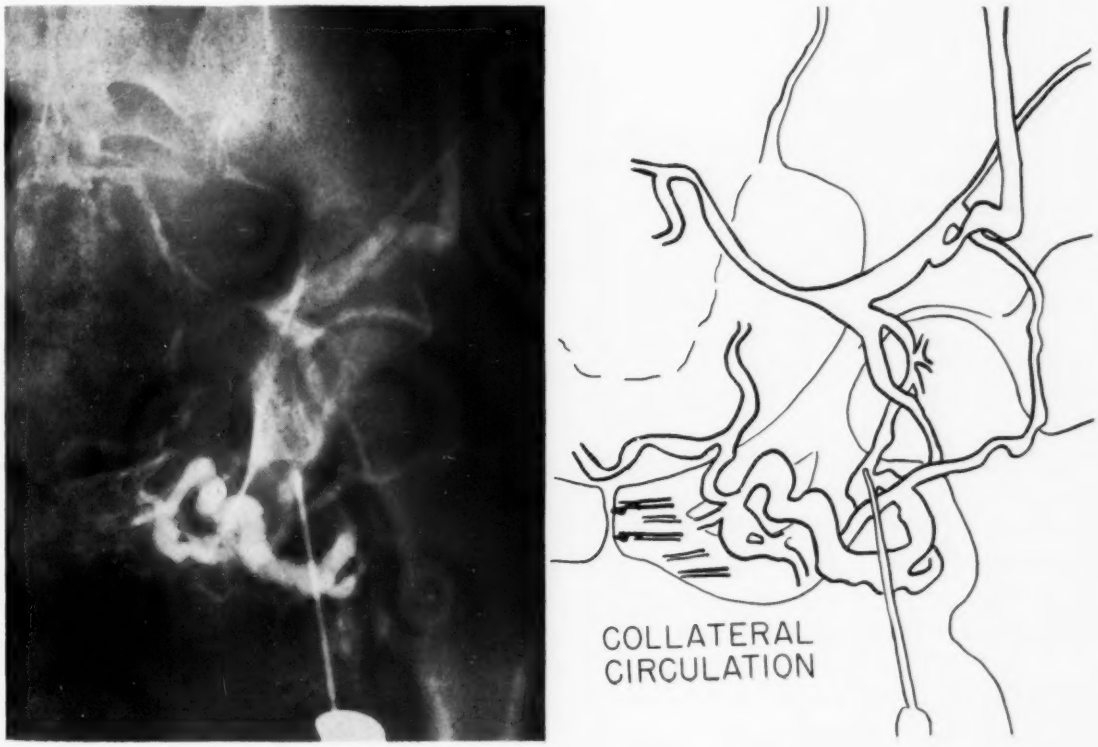


FIG. 7.

A diagnosis of carcinoma of the cervix, LON II, was made on this forty-seven year old woman, and she was treated with radium and parametrial Au^{198}.

The venogram demonstrates indentations on the left common iliac, left external iliac, left hypogastric and right common iliac veins due to lymph nodes with metastatic carcinoma.



tomy after completion of radiation therapy on those patients with LON III carcinoma of the cervix.[16] Initially, venography was performed on these patients after completion of the radiation therapy so that correlation with the pathology would be accurate. At present the roentgen examination is made before the initiation of any therapy, and if there are demonstrable abnormalities in the venous system these patients have repeat venograms before lymphadenectomy.

In our series of 23 proved cases, 14 had no distortion of the venous system. In 13 of these 14 cases, there was no gross or microscopic evidence of tumor in any of the lymph nodes. In 1 case a microscopic focus of cancer was found in a small lymph node. In the 9 proved cases with abnormal venograms, 7 had gross and microscopic evidence that confirmed our findings. The other 2 patients received radium and betatron therapy after the venographic demonstration of metastases and subsequent lymphadenectomy, which showed enlarged lymph nodes at the site of the distortion. Histologic examination revealed marked irradiation effect without evidence of tumor.

CONCLUSIONS

1. Pelvic venography is a safe and accurate procedure.

2. Lymph node metastases can be demonstrated by this technique.

3. Excretory pyelograms can be obtained with this same procedure.

4. Pelvic venography is a satisfactory method to study: (a) the frequency of lymph node involvement, (b) the frequency of the eradication of these lymph nodes by irradiation, and (c) the dosage necessary.

In these ways it promises to be of value in the determination of therapeutic regimes for carcinoma of the cervix.

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THE USE OF A VAGINAL APPLICATOR AS AN ADJUNCT TO THE TREATMENT OF CARCINOMA OF THE CERVIX*

By JOSEPH E. WHITLEY,† M.D., DAMON D. BLAKE, M.D., RICHARD L. WITCOFSKI, M.S., *and* I. MESCHAN, M.D.
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MOST commonly employed cervical applicators and external therapy techniques for treatment of carcinoma of the cervix do not deliver an adequate dose to the significant vaginal extensions of this tumor. A tubular applicator is the time-honored answer to this problem.[1] Until recently it has been used in our department in the form of a tubular source inside a wooden cylinder. The original description of our particular design was published in 1956.[2] This wooden applicator had the advantage of simplicity of design; however, it had to be covered at each application with a rubber sheath; and it lacked stability, durability, and some of the safety features incorporated in our present model. The new applicator, of all metal construction, can be autoclaved, does not need a rubber sheath, and requires less handling, thus reducing exposure to personnel.

DESCRIPTION

The applicator (Fig. 1) consists of a hollow aluminum cylinder with over-all dimensions of 8.5 cm. × 3 cm. with an outside wall thickness of approximately 2 mm. The central cylinder, which holds the low intensity cobalt capsules, is bored exactly to fit their outside diameter and has a wall thickness of 2 mm. A set screw is employed to close the central cylinder once it is loaded. A 20 cm. handle is available with which to grasp the applicator after loading.

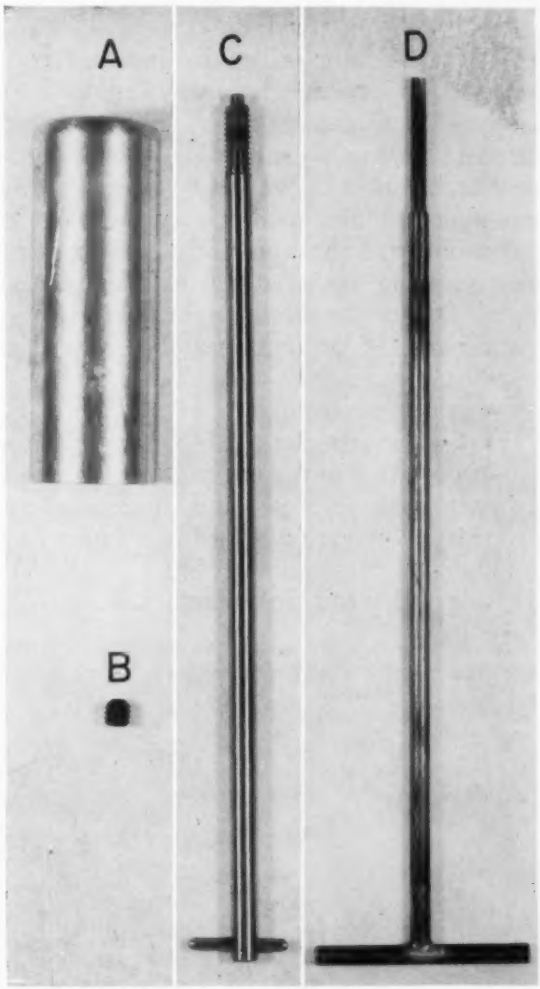

FIG. 1. The disassembled applicator consisting of: A, tube; B, set screw; C, handle; D, wrench for removing set screw.

INDICATIONS

We have elected to use the above described applicator in any carcinoma of the cervix with vaginal extension beyond the upper one third of the vagina. In addition to our usual work-up for carcinoma of the

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cervix, each patient is cystoscoped, urethroscoped, and proctoscoped to determine any invasion of these adjacent organs by the vaginal extension. The discovery of such involvement does not contraindicate the use of this applicator; however, it does increase the incidence of fistulae in the corresponding organ.

METHOD

The applicator is usually inserted concomitantly with urethroscopy and cystoscopy. Once the bladder, rectum, and urethra have been evaluated, the cylinder is introduced into the vagina by means of the metallic handle. Most vaginas readily accommodate the applicator and in very few patients are relaxing incisions necessary. Two or three sutures are used to approximate the labia majora. The handle is then unscrewed from the cylinder. A Foley type catheter containing 5 cc. of 5 per cent NaI is left in place in the bladder.

The position of the applicator is checked in each case with pelvic roentgenograms using a radiopaque medium in a Foley bag and barium in the rectum (Fig. 2, *A* and *B*). It is desirable to place a metal skin clip on the vagina at the point of lowest extension of the tumor, as well as on the lip of the cervix.

DOSAGE

Low intensity, full and half-strength cobalt 60 capsules are used in the cylinder. They are of the stainless steel type with an over-all diameter of 3 mm., wall thickness of 0.5 mm., over-all length 1.6 cm., and an active length of 1.0 cm. Their strengths at this time are approximately 8 and 4 mc. Four capsules are loaded into the applicator according to the dosage pattern desired (Table 1 and Fig. 3). In actual clinical practice the "ideal" distribution is most frequently employed. The loaded applicator is allowed to remain in the vagina for approximately five to six days to deliver 6,000 r_γ to the surface.

The dose to various points about the applicator may be obtained for various dosage patterns by multiplying the total mc dose by the appropriate factor in Table 1. This table was calculated from cumulative summations of each source, neglecting absorption of the aluminum, but including self absorption by the capsules.

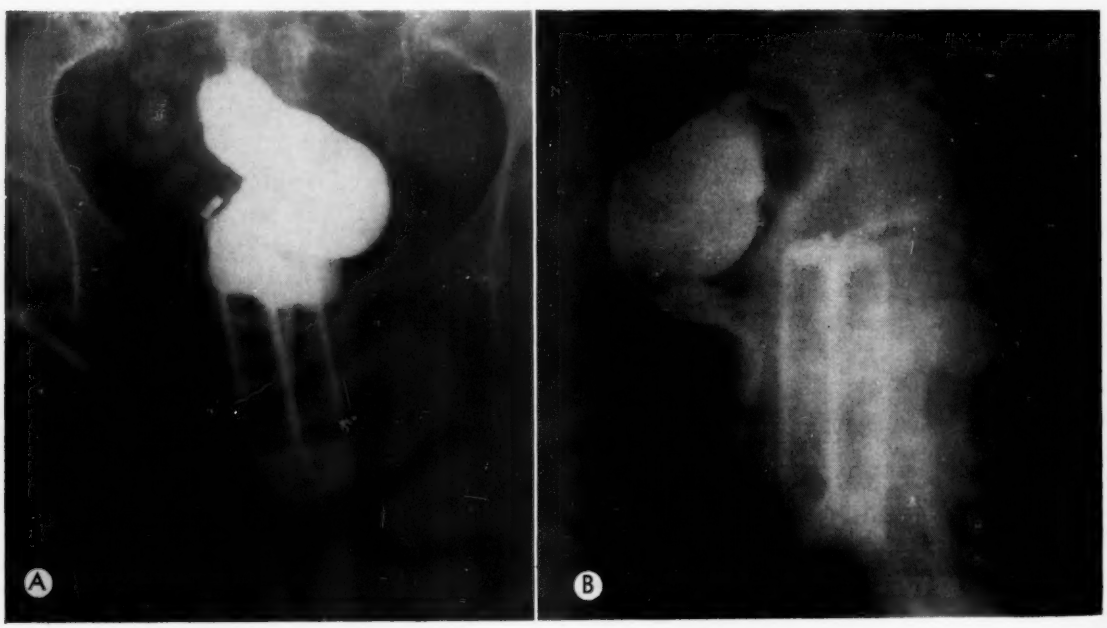

FIG. 2. Typical (*A*) anteroposterior and (*B*) lateral pelvic roentgenograms.

Table I

DOSAGE CALCULATIONS FOR THE APPLICATOR LOADED WITH FULL AND HALF STRENGTH COBALT 60 CAPSULES IN VARIOUS PATTERNS*

Loading	Points												
	A	B	C	D	E	F	A′	B′	B″	C′	D′	E′	F′
Uniform	2.03	1.40	2.46	3.01	3.01	2.46	.62	.58	0.82	1.19	1.45	1.45	1.19
End Load	3.10	1.83	3.08	2.95	2.61	2.06	.91	.69	.98	1.36	1.45	1.32	1.04
Double End Load	2.68	1.73	3.02	3.39	2.63	1.89	.81	.68	.97	1.38	1.55	1.34	.99
Ideal Load	2.59	1.58	2.65	2.63	2.63	2.65	.79	.61	1.87	1.21	1.34	1.34	1.21

* Total mc of the capsules × appropriate factor above = r per hour at point x.
= is one full strength capsule.
– is one half strength capsule.

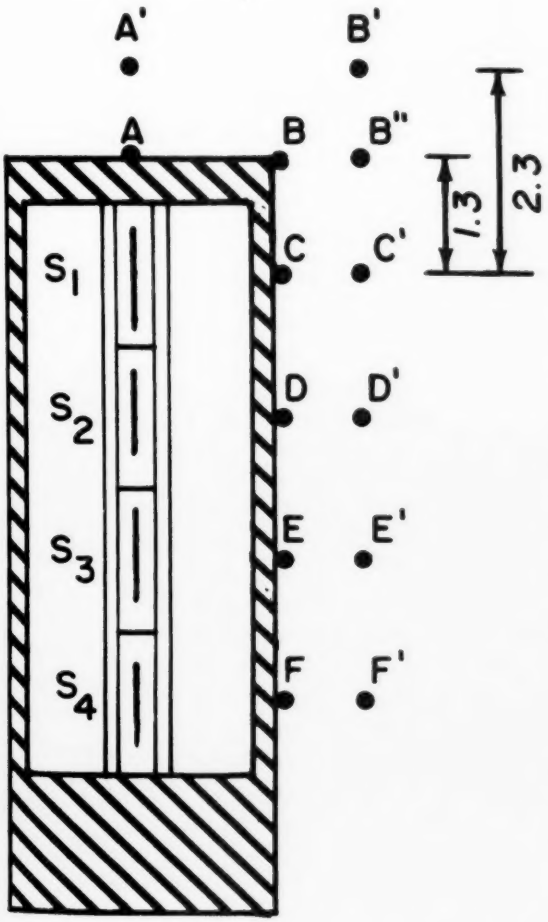

Fig. 3. Cross-sectional drawing of applicator with points corresponding to those in Table 1. Points A through F are on the surface of the applicator. Points A′ through F′ are 1 cm. from the surface.

In the usual application, the posterior bladder and the anterior rectal serosa receive no more than 50 per cent of the dosage administered to the surface of the applicator, due to the rapid fall-off, and that dosage is to only a narrow strip. Difficulty with excessive dosage to the bladder and rectum may be encountered by combining this type of application with some techniques of external therapy, but not with the traditional, separated, straight-on anterior and posterior pelvic fields. We have found that such an application does not interfere with the use of the usual tripartite applicator. The areas where the dose patterns may overlap are the fornices and cervix, which are relatively radioresistant in clinical practice. Thus far, in our experience, the applicator has not significantly raised the incidence of complications in the treatment of carcinoma of the cervix.

DISCUSSION

We believe that the above described applicator is a useful adjunct in the treatment of carcinoma of the cervix with vaginal extension, and find this technique practical and applicable in the great majority of these cases. It is uncommon in our experience for a case to require an individual mold.[3] Other sizes of this model are planned for the exceptional cases we may encounter in the future.

SUMMARY

A description of an aluminum "broomstick" vaginal applicator for use in the treatment of vaginal extension of carcinoma of the cervix is given. Indications and techniques for its use are discussed.

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COBALT 60 TUMOR TREATMENT TIME AND "SKIN" DOSAGE CHARTS*

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IN THE treatment of tumors with cobalt 60 teletherapy units, the skin dose is no longer a limiting factor in delivering a sufficient dose to the tumor, especially when two or more ports are used. Therefore, tables which give the time of treatment for 100 r, at various depths in tissue, are useful. It is also desirable to know the dose which the skin receives during this treatment time. The "skin" dose is the maximum dose received at about 6 mm. below the surface where electron equilibrium is established.

These figures are given in Table 1, a treatment time and "skin" dosage chart for 80 cm. source skin distance (S.S.D.). The time in minutes to give 100 r at a depth is charted against that depth for the given field size. The "skin" dose for the number of minutes the patient is exposed, listed in the column headed "Min.," is given in the adjoining column headed "Max. r". For example, if the center of the tumor is 7 cm. below the surface and the field size is 200 sq. cm., it will take 5.14 minutes to give 100 r to this depth. The Max. r 0.6 cm. below the skin or so called "skin" dose will be 141 r. The time has been kept in minutes, tenths and hundredths of a minute instead of minutes and

TABLE I

TREATMENT TIME AND "SKIN" DOSAGE CHART
80 cm. S.S.D.

Time in minutes to give 100 r tumor dose at depth and "skin" dose, Max. r, for 100 r at depth
Output 27.2 r/min. at 80 cm. S.S.D.

Depth in cm.	Area in sq. cm.									
	25		50		100		200		400	
	Max. r	Min.	Max. r	Min.	Max. r	Min.	Max. r	Min.	Max. r	Min.
0.6	100	3.72	100	3.72	100	3.65	100	3.63	100	3.63
2.0	108	4.01	107	3.97	107	3.90	107	3.88	107	3.88
3.0	116	4.29	114	4.22	112	4.10	113	4.07	111	4.05
4.0	124	4.58	122	4.51	119	4.38	119	4.32	117	4.27
5.0	134	4.96	131	4.84	127	4.65	125	4.55	123	4.48
6.0	144	5.37	143	5.25	136	4.97	133	4.84	131	4.70
7.0	156	5.80	150	5.55	146	5.32	141	5.14	139	5.04
8.0	169	6.25	162	5.99	157	5.75	151	5.49	147	5.34
9.0	183	6.77	174	6.43	167	6.11	161	5.74	156	5.66
10.0	198	7.10	181	6.72	179	6.55	173	6.22	165	6.02
11.0	214	7.96	203	7.52	192	6.91	184	6.70	177	6.25
12.0	231	8.54	220	8.13	206	7.55	197	7.13	188	6.81
13.0	252	9.46	236	8.75	222	8.13	210	7.60	199	7.13
14.0	271	10.01	256	9.46	239	8.77	225	8.14	212	7.73
15.0	293	10.82	275	10.20	257	9.44	249	8.65	227	8.16

* From the Radiation Therapy Department of the Presbyterian Hospital in Newark, New Jersey, a unit of the United Hospitals of Newark.

seconds because it is easier to multiply this figure by multiples of 100 r to compute the time for the required dose. The faces of the control timers can be graduated in minutes, tenths and hundredths of a minute. This obviates the need to transpose into minutes and seconds, a general source of error in calculation.

In these computations no allowance has been made for the change of output in air with field size. The output which has been usedis that for a 10×10 cm. field. The difference between this and the output for other fields is less than 5 per cent. The 0.6 cm. depth is considered as if it were at the source skin distance of 80 cm. Allowance, however, has been made for backscatter. The times have been calculated by using depth dosage data of Johns, Epp, Cormack and Fedoruk.[1] If one wanted a more accurate table, the actual output for the given field size could be used in the calculation.

Table I makes it very easy to determine the time for a required tumor dose at a given depth and to find the "skin" dose without having to do the calculation from depth dose tables each time.

Similar tables have been calculated for a S.S.D. of 50 cm. (Table II) and 100 cm. (Table III). The 100 cm. distance is used with one of our Co^{60} machines when a field dimension larger than 20 cm. is needed, as in the supraclavicular field for breast work on a large patient.

The "skin" dose as listed in these tables remains the same for all machines used at the given distance, since this depends only on the depth dose for the given field size. This is so because the dose that the "skin" receives when 100 r is delivered to the specified depth depends only on the per cent depth dose and depth dose is independent of type of machine. Of course, the depth dose varies with the source skin distance

TABLE II

TREATMENT TIME AND "SKIN" DOSAGE CHART

50 cm. S.S.D.

Time in minutes to give 100 r tumor dose at depth and "skin" dose, Max. r, for 100 r at depth

Output 43.3 r/min. at 50 cm. S.S.D.

Depth in cm.	Area in sq. cm.									
	20		50		100		200		400	
	Max. r	Min.	Max. r	Min.	Max. r	Min.	Max. r	Min.	Max. r	Min.
0.5	100	2.32	100	2.32	100	2.30	100	2.26	100	2.26
1.0	104	2.40	103	2.38	103	2.34	102	2.32	102	2.32
2.0	112	2.57	110	2.52	109	2.49	109	2.46	108	2.45
3.0	122	2.80	119	2.74	117	2.69	116	2.64	115	2.60
4.0	132	3.04	128	2.94	126	2.86	124	2.80	123	2.78
5.0	144	3.30	138	3.17	135	3.10	133	2.99	131	2.94
6.0	157	3.60	150	3.44	146	3.34	143	3.20	139	3.15
7.0	171	3.94	163	3.76	158	3.58	153	3.45	149	3.37
8.0	188	4.30	178	4.07	171	3.90	164	3.72	160	3.58
9.0	206	4.73	194	4.44	186	4.13	178	4.05	170	3.84
10.0	225	5.15	211	4.86	201	4.59	191	4.32	182	4.12
11.0	247	5.63	230	5.27	218	4.98	207	4.67	195	4.42
12.0	270	6.17	250	5.74	237	5.43	222	5.00	209	4.70
13.0	295	6.79	272	6.25	256	5.85	240	5.27	224	5.06
14.0	322	7.39	297	6.81	278	6.35	259	5.80	240	5.41
15.0	351	8.08	324	7.44	301	6.87	278	6.26	256	5.78

TABLE III

TREATMENT TIME AND "SKIN" DOSAGE CHART
100 cm. S.S.D.

Time in minutes to give 100 r tumor dose at depth and "skin" dose, Max. r, for 100 r at depth
Output 17.4 r/min. at 100 cm. S.S.D.

Depth in cm.	Area in sq. cm.			
	200		400	
	Max. r	Min.	Max. r	Min.
0.6	100	5.80	100	5.80
1	101	5.87	101	5.87
2	106	6.15	105	6.13
3	111	6.43	110	6.39
4	116	6.75	115	6.68
5	123	7.12	121	7.04
6	129	7.50	128	7.42
7	137	7.95	134	7.80
8	145	8.42	142	8.22
9	154	8.95	150	8.69
10	165	9.59	159	9.25
11	176	10.20	168	9.75
12	187	10.85	178	10.30
13	198	11.53	189	10.97
14	212	12.25	200	11.61
15	225	13.02	212	12.35
16	239	13.89	225	13.03
17	255	14.78	238	13.79
18	272	15.73	252	14.61
19	289	16.77	267	15.49
20	307	17.78	282	16.34

Note: Calculated by inverse square law from 80 cm. S.S.D.

and field size. The time to deliver the 100 r to a specified depth will depend on the output of the machine and therefore will vary from one machine to another. But once the 100 r is delivered the skin dose will be the same.

The time in minutes for any cobalt 60 machine for an 80 cm. S.S.D., depth, and field size can be calculated from that listed in Table 1. For example, if a machine at a S.S.D. of 80 cm. has an output of 38.4 r/min., then the time to give 100 r to a depth of 8 cm. for a field size of 50 sq. cm., T_8, of that machine, is to, t_8, of the given chart inversely as the respective outputs.

$$\frac{T_8}{t_8} = \frac{\text{Output on chart}}{\text{Output}}$$

$$\frac{T_8}{5.99} = \frac{27.2}{38.4}$$

$$T_8 = 4.24 \text{ min.}$$

The same method of calculation can be used for the 50 cm. S.S.D. and 100 cm. S.S.D. and when the charts are changed to allow for decay of the cobalt 60.

Treatment time charts have also been compiled for rotation therapy. The average thickness of the patient in centimeters is charted versus the time for delivery of 100 r to the center of rotation (Table IV). The

TABLE IV

ROTATION THERAPY
TREATMENT TIME CHART
55 cm. S.A.D

Time in minutes to give 100 r tumor dose for different thicknesses
Output 35.8 r/min. at 55 cm. S.A.D.

Average Thickness in cm.	Area in sq. cm.				
	50	100	150	200	400
	Min.	Min.	Min	Min.	Min.
10	3.24	3.14	3.10	3.06	2.97
11	3.31	3.20	3.16	3.10	3.01
12	3.40	3.29	3.22	3.16	3.08
13	3.48	3.35	3.29	3.22	3.14
14	3.59	3.44	3.37	3.31	3.18
15	3.68	3.52	3.44	3.37	3.24
16	3.78	3.61	3.52	3.46	3.31
17	3.88	3.70	3.61	3.54	3.37
18	3.99	3.80	3.70	3.63	3.46
19	4.14	3.88	3.80	3.72	3.52
20	4.23	3.99	3.91	3.80	3.61
21	4.36	4.10	3.99	3.88	3.68
22	4.49	4.21	4.10	3.99	3.76
23	4.64	4.33	4.21	4.10	3.84
24	4.76	4.44	4.31	4.21	3.93
25	4.91	4.58	4.42	4.31	4.02
26	5.04	4.70	4.55	4.42	4.10
27	5.19	4.83	4.65	4.53	4.18
28	5.34	4.98	4.78	4.64	4.27
29	5.50	5.10	4.91	4.76	4.38
30	5.66	5.25	5.04	4.87	4.46

average thickness in centimeters is twice the average depth of the center of rotation or center of the tumor. The reason for using average thickness will be explained shortly. The time of treatment was calculated by using tumor to air, T/A, ratios for the given depth and field size as described by Johns, Morrison and Whitmore.[2]

The skin dose cannot be derived as easily as for fixed beam therapy but may be obtained from Co^{60} isodose curves for rotation.

The times of treatment for any cobalt machine, including source axis distances (S.A.D.) other than 55 cm., may be obtained from Table IV by formulating a proportion similar to that given above for fixed port therapy and using the output at the center of rotation. This is so because the T/A ratios are independent of distance, from 40 cm. to 100 cm.

We have found that less than 4 per cent error is made when the averages of the anteroposterior and lateral dimensions of a patient are used in calculating the T/A ratio, instead of finding the average T/A ratio from those corresponding to the depth of the center of rotation for twelve sectors. This obtains even when the tumor center is not symmetrically situated in the patient. However, this does in no way obviate the necessity of accurately localizing the tumor

TABLE V

OPPOSING PORT THERAPY
TREATMENT TIME AND "SKIN" DOSAGE CHART
55 cm. S.A.D.

Time in minutes to treat each port, to give 100 r tumor dose from two opposing ports and "skin" dose, Max. r, including exit dose for 100 r at 55 cm. S.A.D.
Output 35.8 r/min. at 55 cm. S.A.D.

Thickness in cm.	Area in sq. cm.									
	50		100		150		200		400	
	Max. r	Min.	Max. r	Min.	Max. r	Min.	Max. r	Min.	Max. r	Min.
10	107	1.62	106	1.57	105	1.55	104	1.53	103	1.49
11	109	1.65	107	1.60	106	1.58	105	1.55	104	1.51
12	111	1.70	109	1.64	108	1.61	107	1.58	106	1.54
13	113	1.75	111	1.67	110	1.64	109	1.61	108	1.57
14	116	1.80	113	1.72	112	1.68	111	1.65	109	1.59
15	118	1.84	116	1.77	114	1.72	113	1.68	111	1.62
16	122	1.89	118	1.81	117	1.77	116	1.73	113	1.65
17	125	1.94	121	1.85	120	1.81	119	1.78	115	1.68
18	129	2.00	125	1.90	123	1.85	122	1.82	118	1.73
19	133	2.06	128	1.94	127	1.90	125	1.86	121	1.77
20	138	2.22	132	1.99	131	1.95	129	1.90	125	1.81
21	143	2.18	137	2.05	135	1.99	133	1.94	128	1.84
22	148	2.24	141	2.11	139	2.05	137	1.99	132	1.88
23	154	2.32	147	2.17	144	2.11	141	2.05	136	1.92
24	160	2.38	152	2.22	149	2.16	146	2.11	140	1.96
25	167	2.46	158	2.28	154	2.21	152	2.16	144	2.00
26	174	2.52	164	2.35	160	2.27	157	2.21	149	2.05
27	181	2.60	171	2.42	167	2.32	163	2.26	154	2.10
28	189	2.67	179	2.49	173	2.40	169	2.31	159	2.14
29	198	2.76	186	2.55	181	2.46	176	2.38	165	2.19
30	208	2.83	195	2.62	189	2.52	184	2.44	181	2.23

and its center. It does make dosage calculation for rotation therapy with Co^{60} simpler and allows charts to be made which can easily be used. A word of warning—the same short cut may not be used for the 200 kv. region. Here errors as large as 20 per cent would occur.

It is often convenient with the patient lying on the treatment table to place the center of the tumor at the center of rotation and treat the tumor through two opposing ports, anterior and posterior, or two lateral ports. Table v is useful for this type of treatment. It gives the treatment time for each of the two ports in order to deliver a tumor dose of 100 r (50 r from each). The "skin" dose includes the exit dose. The "skin" dose remains the same for all cobalt machines with a S.A.D. of 55 cm. and the center of the tumor at the center of rotation. The assumption has been made that the center of the tumor is equidistant between the two surfaces. If the center is slightly asymmetric, the error is not too great. The time of treatment for any machine at a S.A.D. of 55 cm. with a known output may be calculated from the times given in the chart by using the proportion previously given.

These tables have been tested by a number of radiologists who have cobalt 60 machines and were found to be very useful.

SUMMARY

1. Treatment time and "skin" dosage charts for different field sizes are given for 80 cm., 50 cm., and 100 cm. source skin distances. The "skin" dose remains the same for all machines for the given S.S.D., depth, and field size.

2. A treatment time chart for rotation therapy is given in which the time for 100 r is listed versus the average thickness of a patient for different field sizes. This chart is applicable for source axis distances from 40 cm. to 100 cm.

3. A table is given for use with opposing port therapy at 55 cm. S.A.D. The time to treat each port, for 100 r tumor dose, and the "skin" dose including exit dose are charted versus the thickness of the patient for different field sizes.

4. A method is described for calculating the treatment times for any cobalt 60 therapy machine from the given tables.

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FOCUSED GRID TELECOBALT THERAPY*

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A RELATIVELY large number of hopelessly advanced cancer cases are referred to our department of radiotherapy. These patients have such advanced disease that the surgeons cannot undertake removal of the tumor and expect a postoperative survival. A radiotherapist, knowing from experience that conventional treatment with homogeneous radiation does not inevitably alleviate pain and prolong life, dreads the referral of such cases and often refuses to treat them. A course of therapy by conventional methods usually involves four to six weeks of hospitalization or outpatient visits. Toward the end of the treatment, the patient may still suffer considerable discomfort from both the tumor and the effects of treatment. Sorely needed was a practical and efficient method of palliation that would permit the administration of large doses of radiation in a short span of time with minimum side reactions and maximum relief of symptoms. An effective method would make it possible to: (1) deliver large doses of radiation; (2) shorten the treatment period (ten days to two weeks); (3) cause rapid tumor regression; (4) maintain anatomic and physiologic integrity of organs involved; (5) minimize radiation sickness (nausea, vomiting, malaise); and (6) minimize skin reaction.

In searching for a way to accomplish these objectives, we decided at the beginning of 1957 to modify our telecobalt therapy by the use of a grid. The idea was suggested by the observation of some patients who received excellent palliation from 250 kv. peak therapy with grids. An analogy can also be drawn from the effects of radium or cobalt needle implantation.[1,2,3]

Our modification of the conventional telecobalt therapy involves the use of a grid fashioned from a block of lead 5.4 cm. thick which is perforated by cylindrical holes diverging toward the patient. The lead block is attached to the treatment cone, and a perforated piece of metal is attached to the grid to permit registry of the grid pattern with successive treatments (Fig. 1 and 2).

CLINICAL MATERIAL

From May, 1957 through December, 1958, we treated 87 patients with focused grid telecobalt therapy. The youngest patient was three and one-half years of age; the oldest eighty-three. The mean age was fifty-nine years. Forty-six patients were white and 41 were Negro. Forty-nine were

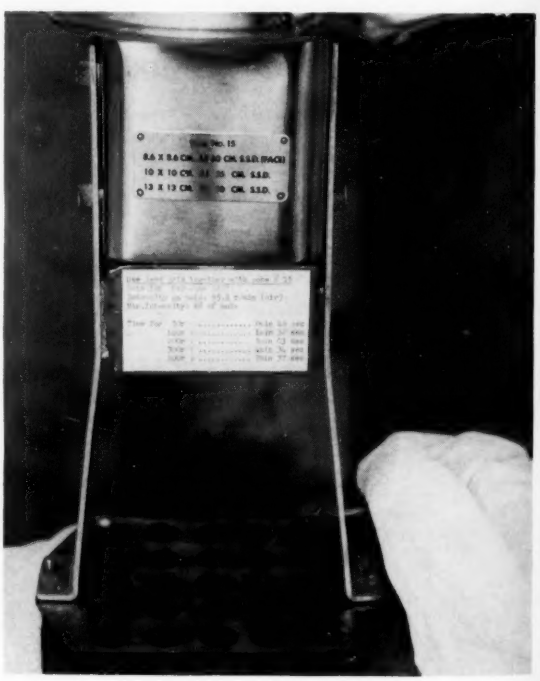

FIG. 1. Focused grid in position for treatment.

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Fig. 2. Detail of focused grid and metal register.

men and 38 women. During the time of this study, 45 patients remained alive and 42 died. There were 18 cases of carcinoma of the bladder, 25 cases of carcinoma of the lung, 20 cases of carcinoma of the female genital tract, 17 cases of carcinoma of the head and neck including 3 cases of carcinoma of the esophagus, and 7 cases of miscellaneous malignancies (Table I). A more detailed breakdown of the number and types of carcinoma treated is given in Tables II, III, and IV.

In order to analyze whether or not relief was obtained from the treatments, a palliation index was devised. The palliation index (PI) is the product of two factors, namely, the palliation factor (P) and the number of months of survival (T).

The palliation factor (P) was designated by four grades of relief ranging from P-0 to P-3. Palliation factor 3 (P-3) meant that the patient had received maximal benefit and was able to conduct his life in a manner similar to his mode of living prior to illness. Palliation factor 2 (P-2) meant that the patient had a good result in terms of considerable alleviation of symptoms and regression in the size of the tumor. Palliation factor 1 (P-1) meant that the patient had received appreciable benefit in terms of alleviation of symptoms, regression of the size of the tumor, or both. No palliation, or P-0, meant that the patient had received no benefit, or may indeed have gotten worse.

To define the palliation factor objectively, it was decided to grade the symptoms and the status by physical examination and by laboratory, roentgenographic, operative, and pathologic findings obtained after completion of therapy. As the findings changed during follow-up, the individual

Table I

VITAL STATISTICS

Origin of Carcinoma	No. of Patients	Mean Age (yr.)	Age Range (yr.)	Race		Sex		Living	Dead
				White	Negro	Male	Female		
Bladder	18	65	44–76	11	7	8	10	9	9
Lung	25	58	35–80	17	8	24	1	12	13
Female Genital	20	56	25–83	4	16	0	20	13	7
Head and Neck	17	67	39–82	9	8	12	5	6	11
Miscellaneous	7	51	3·5–74	5	2	5	2	5	2
Total	87	59	3·5–83	46	41	49	38	45	42

TABLE II

FEMALE GENITAL TRACT

Site of Origin	No. of Patients
Carcinoma of Endometrium	9
Carcinoma of Cervix (1 sarcoma and 1 adenocarcinoma)	9
Carcinoma of Ovary	2
Total	20

factors were averaged; this resulted in a mean palliation factor which was judged the fairest approximation by conference opinion.

The survival time (T) was calculated in months of survival. If the patient was still living at the end of the time of analysis (December 31, 1958), a plus was included with the palliation index. If the patient was dead at the end of the period of analysis, the palliation index was given without the additional sign.

Analysis of the palliation factor (Table v) reveals that of the 87 patients, 51 (59 per cent) received appreciable palliation or better (P-1, 2 and 3). No palliation was observed in 36 patients (41 per cent). A further breakdown shows that 30 patients (35 per cent) received appreciable relief (P-1) and 12 patients (14 per cent) received good palliation (P-2). Nine patients (10 per cent) had excellent palliation (P-3).

TABLE III

HEAD AND NECK

Site of Origin	No. of Patients
Carcinoma of Pharynx	1
Carcinoma of Tonsil	2
Carcinoma of Oral Cavity	1
Carcinoma of Hard Palate	2
Carcinoma of Floor of Mouth	1
Carcinoma of Buccal Mucosa	1
Carcinoma of Gingiva	1
Carcinoma of Sinuses	2
Carcinoma of Skin	2
Metastases to Neck	1
Carcinoma of Esophagus	3
Total	17

TABLE IV

MISCELLANEOUS MALIGNANCIES

Site of Origin	No. of Patients
Prostate	1
Colon	1
Hodgkin's Disease	1
Kidney	1
Pancreas	1
Scrotum	1
Lymphosarcoma	1
Total	7

Successful palliation from grid therapy varied considerably with the site of origin of the carcinoma (Table VI). The best palliative results were obtained in carcinoma of the bladder (78 per cent), and the least palliative results in carcinoma of the lung (only 36 per cent benefited). Of the patients who had female genital tract carcinoma, 65 per cent were successfully treated. Of the patients with carcinoma of the head and neck, 59 per cent experienced relief, and 71 per cent of the miscellaneous malignancies were successfully treated.

In terms of human suffering and months of survival, it is noted (Table VII) that there were 101 months of a total of 438 survival months for the entire group without palliation. In other words, 23 per cent of the total months survived can be considered a treatment failure. Thirty patients survived 203 months at the appreciable palliation factor of P-1, yielding a total of 46 per cent of the months survived at this level of palliation. Good palliation (P-2) was achieved in 12 patients for 52 months, 12 per cent of the months survived. Nine patients had excellent palliation (P-3) and survived 82 months, which is 19 per cent of the total months survived. Undoubtedly, in a series with such advanced cases of cancer, even if the patients had survived 438 months without treatment, palliation could hardly be expected. It can be concluded that the focused grid telecobalt

TABLE V

PALLIATION AND SURVIVAL BY CANCER SITE

Cancer Site	Palliation Factor (P)							
	P-0 None		P-1 Appreciable		P-2 Good		P-3 Excellent	
	No. of Patients	Total Survival (mo.)	No. of Patients	Total Survival (mo.)	No. of Patients	Total Survival (mo.)	No. of Patients	Total Survival (mo.)
Bladder	4	6	9	49	3	12	2	15
Lung	16	37	5	16	4	13		
Female Genital	7	29	8	87	1	1	4	44
Head and Neck	7	24	6	35	3	17	1	5
Miscellaneous	2	5	2	16	1	9	2	18
Total	36	101	30	203	12	52	9	82

TABLE VI

SUCCESSFUL PALLIATION FROM GRID THERAPY BY CANCER SITE

Cancer Site	Total No. of Patients	Appreciable Palliation or Better (P-1, 2, 3)		Good to Excellent Palliation (P-2, 3)	
		No. of Patients	Per Cent	No. of Patients	Per Cent
Bladder	18	14	78	5	28
Lung	25	9	36	4	16
Female Genital	20	13	65	5	25
Head and Neck	17	10	59	4	24
Miscellaneous	7	5	71	3	43
Total	87	51	59	21	25

therapy was successful in producing some relief of symptoms in 51 patients for 337 months, or 77 per cent of the total time survived.

From Table VI, it appears that patients with cancer of the lung are less likely to receive benefit than those with other types of cancer. Only 9 of 25 patients (36 per cent) with lung cancer received successful palliation, while 14 of 18 persons with bladder cancer (78 per cent) were successfully treated. A low level of success for palliation could militate against the use of focused telecobalt grid therapy in a particular type of cancer. Certainly, if we excluded all the cases of carcinoma of the lung, the palliation results in our series would be strikingly improved. However, from a clinical viewpoint, the physicians in our radiotherapy department consider that even a level of

TABLE VII

TOTAL SURVIVAL IN MONTHS AND AMOUNT OF PALLIATION

No. of Patients	Palliation	Total Survival	
		Months	Per Cent
36	P-0 (none)	101	23
30	P-1 (appreciable)	203	46
12	P-2 (good)	52	12
9	P-3 (excellent)	82	19
Total 87	Total Months of Survival	438	

appreciable palliation in one-third of the patients with advanced cancer of the lung is worthwhile.

A tabulation of pertinent clinical data by cancer site for individual patients is given in Tables VIII, IX, X, XI, and XII.

From the palliation index (PI), it is easy to recognize patients who received extraordinary benefit and those who received little or none. Following are reports of 3 patients who benefited considerably from this mode of therapy and 3 patients who were treatment failures.

REPORT OF CASES

CASE I. MS 14-60-39. *Transitional Cell Carcinoma of the Bladder.* This sixty-five year old housewife, a patient of Dr. James Headstream, presented with a three months' history that was compatible with cystitis and hematuria. Operation in June, 1957, consisted of fulguration and removal of a portion of a transitional cell carcinoma of the bladder.

On January 7, 1958, she returned for a check-up examination and complained of deep pelvic discomfort with "bearing down sensation." Bimanual examination revealed a large extravesical extension of the tumor on the left.

TABLE VIII

FOCUSED GRID TELECOBALT THERAPY CLINICAL DATA—BLADDER CARCINOMA

No.	Unit No.	Age, Race, Sex	Type of Cancer	Stage	Total Dose at Hole Center	First Treatment Date	Died	Palliation Factor (P)	Survival Time (T) (mo.)	Palliative Index (P ×T)*	Remarks
1	13-49-03 CC	66 NM	Adenocarcinoma of bladder	III	12,000 r	6/13/57	9/10/57	2	3	6	Ureters transplanted before therapy; pain improved
2	13-05-65 NG	69 WF	Carcinoma of bladder	IV	12,000 r	6/19/57	8/22/57	1	2	2	Tumor showed marked shrinkage
3	13-28-29 PW	74 NF	Adenocarcinoma of bladder	III	2,400 r (incomplete)	7/ 2/57	7/ 5/57	0	0	0	Received only 2 treatments; patient was uremic
4	13-13-54 LW	62 WF	Carcinoma of bladder	III	12,500 r	7/ 9/57		1	17	17+	Tumor recurred but with marked symptomatic improvement
5	13-97-57 EC	66 NF	Adenocarcinoma of bladder	IV	12,000 r	8/30/57	12/15/57	1	3	3	Good relief of pain
6	14-60-39 MS	65 WF	Carcinoma of bladder	III	15,000 r	1/16/58		3	13	39+	Asymptomatic and doing exceptionally well
7	14-86-43 WL	67 WM	Carcinoma of bladder	IV	13,800 r	3/19/58		1	8	8+	Will not return for check-up
8	14-41-76 WN	67 WM	Carcinoma of bladder	IV	12,000 r	3/24/58	9/14/58	1	5	5	Good pretreatment pneumogram
9	11-90-80 MT	76 WF	Carcinoma of bladder	III	12,000 r	4/ 1/58		2	8	16+	
10	08-28-94 JW	73 NM	Carcinoma of bladder	IV	12,000 r	4/ 8/58	8/13/58	1	4	4	Pneumograms on 4/9/58 and 7/1/58 show progression of tumor; since improved
11	15-12-31 NB	71 NF	Carcinoma of bladder	IV	1,000 r (incomplete)	6/ 9/58	9/ 6/58	0	2	0	Incomplete; 1 treatment
12	15-53-04 SC	54 WM	Carcinoma of bladder	IV	12,000 r	8/18/58	12/11/58	1	3	3	
13	15-50-74 CP	71 NF	Carcinoma of bladder	IV	12,000 r	8/22/58		1	4	4+	Asymptomatic except for slight back pain and dysuria
14	15-50-00 LS	69 WF	Carcinoma of bladder with lung metastases	IV	12,000 r	8/22/58		0	4	0+	Had lung metastases; has good pretreatment pneumogram
15	15-45-55 BK	66 NM	Carcinoma of bladder	IV	12,000 r	9/ 2/58		1	3	3+	
16	15-88-88 DS	44 WM	Carcinoma of bladder	III	12,000 r	11/20/58		3	2	6+	No bleeding, no pain; gained 20 lb.
17	15-97-96 ML	54 WF	Carcinoma of bladder	IV	12,000 r	12/10/58	12/17/58	0	0	0	
18	16-00-36 RH	55 WM	Carcinoma of bladder	IV	12,000 r	12/15/58		2	1	2+	Very mild dysuria, otherwise asymptomatic

* + = patient still living at completion of this study (December 31, 1958).

Table IX

FOCUSED GRID TELECOBALT THERAPY CLINICAL DATA—LUNG CARCINOMA

No.	Unit No.	Age, Race, Sex	Type of Cancer	Stage	Total Dose at Hole Center	First Treatment Date	Died	Palliation Factor (P)	Survival Time (T) (mo.)	Palliative Index (P×T)*	Remarks
1	13-56-32 JG	67 NM	Carcinoma of lung		12,500 r	5/22/57	8/ 2/57	1	3	3	Therapy interrupted five weeks; post-therapy moderate expansion of left lung
2	13-56-47 JM	56 NF	Adenocarcinoma of lung		4,800 r (incomplete)	6/17/57	6/29/57	0	0	0	Treatment incomplete
3	14-26-28 JB	80 NM	Carcinoma of lung		10,200 r	10/21/57	1/13/58	2	3	6	
4	14-52-82 RC	53 WM	Carcinoma of lung with metastases		12,000 r	1/ 9/58	3/ 6/58	0	2	0	
5	14-44-70 MW	58 WM	Carcinoma of lung		12,000 r	1/16/58	4/ 9/58	0	2	0	Chest roentgenogram showed worsened condition
6	14-31-08 TM	62 WM	Carcinoma of lung		7,500 r (incomplete)	1/20/58		0	11	0+	Chest roentgenogram showed worsened condition; right lower lobe atelectatic
7	14-55-15 JL	61 WM	Carcinoma of lung		15,000 r	1/27/58		0	10	0+	Little relief; Pancoast's syndrome worse (died 3/8/59)
8	14-63-54 RW	57 NM	Carcinoma of lung		15,000 r	2/12/58	4/21/58	1	2	2	No roentgenographic change
9	14-03-74 AS	47 WM	Carcinoma of lung		12,000 r	2/21/58	3/ 6/58	0	0	0	Lived two weeks
10	14-87-01 LT	35 WM	Carcinoma of lung		7,200 r (incomplete)	3/31/58	4/ 8/58	0	0	0	Cancer with abscess formation
11	Ac-90-62 JW	79 NM	Carcinoma of lung		12,000 r	4/ 7/58		1	8	8+	Progression of tumor; pain improved
12	15-01-00 CT	52 WM	Carcinoma of lung		3,000 r incomplete	4/30/58	5/ 3/58	0	0	0	Lived four days; treatment incomplete
13	14-91-52 OE	48 WM	Carcinoma of lung (mesothelial cell)		12,000 r	5/ 5/58	7/14/58	0	2	0	
14	14-97-37 JP	51 WM	Carcinoma of lung		12,000 r	5/12/58		0	7	0+	Much worse, subjectively and objectively
15	14-97-32 JA	71 WM	Carcinoma of lung		12,000 r	7/31/58		2	5	10+	Gained 23 lb.; able to drive car; regression of lesion
16	15-63-91 GB	63 NM	Carcinoma of lung		12,000 r	9/15/58	10/ 3/58	0	0	0	Survived eighteen days
17	15-54-76 CW	53 WM	Carcinoma of lung		10,800 r	9/30/58		2	3	6+	Improved considerably, subjectively and objectively
18	15-59-84 CH	64 WM	Carcinoma of lung		12,000 r	10/ 8/58		1	2	2+	
19	15-76-47 WM	60 WM	Carcinoma of lung		12,000 r	10/17/58		2	2	4+	
20	A2-75-18 CR	60 NM	Carcinoma of lung		4,800 r (incomplete)	10/24/58	11/ 1/58	0	0	0	Incomplete treatment; died in eight days
21	15-82-66 GH	56 WM	Carcinoma of lung		12,000 r	11/20/58		0	1	0+	Simulated abscess of lung (died 1/29/59)
22	15-90-46 HP	63 WM	Carcinoma of lung		12,000 r	11/24/58		0	1	0+	Roentgenograms showed worsened condition
23	15-92-20 CJ	52 WM	Carcinoma of lung		3,600 r (incomplete)	12/ 5/58	12/14/58	0	0	0	Incomplete treatment; died after nine days
24	15-83-28 FW	46 NM	Carcinoma of lung		12,000 r	12/12/58		0	1	0+	Died 2/16/59
25	15-86-22 SS	62 WM	Carcinoma of lung		12,000 r	12/29/58		1	1	1+	Marked reduction in size of mass

* See footnote to Table VIII.

TABLE X

FOCUSED GRID TELECOBALT THERAPY CLINICAL DATA—FEMALE GENITAL TRACT

No.	Unit No.	Age, Race, Sex	Type of Cancer	Stage	Total Dose at Hole Center	First Treatment Date	Died	Palliation Factor (P)	Survival Time (T) (mo.)	Palliative Index (P ×T)*	Remarks
1	A1-43-03 FW	52 NF	Carcinoma of cervix	III	11,200 r	5/24/57		1	19	19+	Biopsy 11/3/57; irradiation; no tumor; gained 43 lb.; ?recurrence 2/17/58
2	13-48-62 RA	37 NF	Adenocarcinoma of cervix	IV	12,000 r	5/27/57	9/23/57	0	4	0	Lower abdominal discomfort
3	13-52-32 DF	70 WF	Adenocarcinoma of uterus		12,000 r	6/10/57		3	19	57+	½ cm. polyp of endometrium; no gross tumor seen; radiation reaction; did well, remained asymptomatic; hysterosalpingo-oophorectomy 8/23/57
4	13-70-99 RR	32 NF	Carcinoma of cervix	III	12,000 r	6/24/57	5/13/58	0	11	0	Surprisingly little tumor found at operation; viable tumor in specimen; anterior evisceration 9/16/57
5	13-65-54 GG	62 WF	Adenocarcinoma of uterus		12,000 r	7/ 1/57		3	18	54+	From December '57 to January '59 no symptoms; viable, probable adenocarcinoma two months after therapy; hysterectomy 9/13/57
6	13-96-10 MJ	66 NF	Adenocarcinoma of uterus	IV	10,800 r	8/19/57	7/ 4/58	1	11	11	Chest metastases when treated; massive carcinomatosis found in peritoneal cavity at operation; operation Memphis 11/28/57
7	14-22-49 VB	28 NF	Carcinoma of cervix	IV	12,000 r	10/15/57	2/20/58	0	4	0	No response; roentgenograms showed worsening condition
8	14-14-87 MY	65 NF	Adenocarcinoma of uterus		12,000 r	10/22/57		1	15	15+	Wertheim's operation 1/27/58
9	14-45-25 AN	42 NF	Carcinoma of cervix	IV	13,000 r	12/16/57	6/ 3/58	1	6	6	Wertheim's operation; grid therapy on right, homogeneous beam on left
10	14-69-43 JB	50 NF	Carcinoma of cervix	IV	19,000 r	2/10/58		1	11	11+	9/2/58. No complaints; obvious tumor present
11	14-66-36 LM	44 NF	Carcinoma of cervix	IV	15,000 r	2/18/58		1	11	11+	Aortic lymph nodes involved; improved considerably but no recent follow-up
12	14-80-00 EP	50 NF	Carcinoma of cervix	IV	12,000 r	3/10/58		1	9	9+	Grid therapy on right side, homogeneous beam on left side
13	14-89-01 WG	83 NF	Adenocarcinoma of uterus		12,000 r	4/ 7/58		0	6	0+	8/18/58. Swollen feet; granular bleeding lesion on vagina; cancer still present
14	15-09-69 WL	63 NF	Carcinoma of ovary		12,000 r	6/16/58	10/15/58	0	4	0	
15	15-42-07 NM	67 NF	Carcinoma of cervix	IV	12,000 r	8/11/58		1	5	5+	Abdominal bloating; fistula between rectum and vagina 11/17/58
16	15-19-84 MN	81 WF	Adenocarcinoma of uterus		12,000 r	9/ 2/58		3	4	12+	Feels well; vagina stenotic, cervix firm
17	A7-47-33 CM	25 NF	Carcinoma of ovary with metastases to liver and spleen		9,600 r (incomplete)	9/15/58		0	0	0+	Patient did not return for completion of treatment
18	15-42-9c LW	70 NF	Adenocarcinoma of uterus		12,000 r	10/27/58		3	3	9+	4/8/59. No symptoms; excellent condition; large fibroids were found at operation, radical hysterectomy
19	15-72-65 CM	75 NF	Carcinoma of pelvis; probably adenocarcinoma of uterus		12,000 r	12/ 1/58	12/10/58	0	0	0	Died in nine days
20	15-94-00 MS	58 WF	Sarcoma of cervix		12,000 r	12/ 8/58		2	1	2+	Pain in rectum; biopsy, cervicitis, no tumor; excellent regression of mass

* See footnote to Table VIII.

TABLE XI

FOCUSED GRID TELECOBALT THERAPY
CLINICAL DATA—HEAD AND NECK CARCINOMA

No.	Unit No.	Age, Race, Sex	Type of Cancer	Stage	Total Dose at Hole Center	First Treatment Date	Died	Palliation Factor (P)	Survival Time (T) (mo.)	Palliative Index (P×T)*	Remarks
1	A5-84-46 AP	76 NM	Carcinoma of pharynx		12,000 r	12/ 5/58	12/18/58	0	0	0	Patient died before completion of therapy
2	A3-41-92 BF	71 NM	Carcinoma of tonsil		12,000 r	2/14/58		1	11	11+	Died 2/8/59
3	13-68-32 PP	71 WM	Carcinoma of tonsil		5,600 r (incomplete)	9/23/58	11/19/58	0	2	0	
4	15-62-41 WC	66 WM	Carcinoma of hard palate		12,000 r	9/10/58		2	3	6+	Extension into sinuses; residual tumor present but no complaints
5	15-95-68 AP	59 NF	Carcinoma of hard palate		12,000 r	12/ 1/58		0	1	0+	Very resistant tumor; no response
6	15-34-22 BB	75 NM	Carcinoma of floor of mouth		11,000 r	7/21/58	8/20/58	0	1	0	Survived one month
7	14-67-95 RW	73 WF	Carcinoma of buccal mucosa		10,000 r	5/ 8/58	10/ 4/58	1	5	5	Retreatment after conventional therapy
8	14-71-98 NG	67 NM	Carcinoma of gingiva		3,000 r (incomplete)	3/ 3/58	4/20/58	0	1	0	Mandible invaded
9	14-55-54 EW	73 NF	Carcinoma of maxillary sinus		12,000 r	1/ 9/58		0	12	0+	Temporary regression of huge mass
10	14-43-93 TH	68 WM	Carcinoma of maxillary sinus		12,000 r 12,000 r	12/10/57 4/ 7/58	5/12/58	2	6	12	Remarkable visible and roentgen improvement
11	14-37-43 HS	82 WM	Skin carcinoma on face		8,000 r	3/11/58	8/24/58	3	5	15	Dramatic response
12	15-06-02 CS	58 WM	Basal cell carcinoma of ear		12,000 r	5/12/58		2	8	16+	Excellent initial result; recurrence in December, 1958
13	13-24-03 HF	39 NF	Anaplastic carcinoma, metastasis to neck		12,000 r	2/19/58	9/14/58	0	7	0	Probably pelvic primary; lymphangitis lung spread, metastatic to brain
14	14-95-37 VT	59 WM	Carcinoma of oral cavity		12,000 r	4/21/58	7/20/58	1	3	3	
15	13-75-48 EH	56 NM	Carcinoma of esophagus		12,000 r	6/ 4/57	11/24/57	1	6	6	
16	13-75-89 BB	58 WM	Carcinoma of esophagus		12,000 r	7/24/57	10/25/57	1	3	3	Remarkable objective improvement on roentgenograms
17	15-08-45 LB	80 WF	Carcinoma of esophagus		12,000 r	6/ 4/58		1	7	7+	Cervical esophageal carcinoma; tumor regressed; follow-up

* See footnote to Table VIII.

Cystoscopy showed that the left lateral and posterior bladder wall was involved by infiltrating tumor. On microscopic examination, the cells were seen to be highly anaplastic. She was referred for grid therapy.

The following factors were used: Keleket-Barnes telecobalt apparatus; half value layer 12 mm. Pb; 50 cm. skin source distance; field size with grid 13×13 cm.; 1 anterior pelvic portal. From January 16 to 29 the patient received 1,500 r each day to a total of 15,000 r as measured in air in the hole center.

At the conclusion of her treatment there was no definite change, but within a month the symptoms disappeared and the urine was clear. In subsequent follow-up examinations, the patient was considered to be in excellent health without evidence of recurrence (P-3, T-12, PI-36+).

CASE 11. BB 13-75-89 WM 59. *Epidermoid Carcinoma of the Esophagus.* On July 24, 1957, this patient was referred from the State Mental Hospital with a history of chronic cough, weight loss, fever of unknown origin, and general debility. He was suspected of having tuberculosis. It was noted on the ward that he was refusing food and on several occasions had difficulty in swallowing. Regurgitation was also noted. Except for emaciation and fever, the physical examination was nonrevealing. A barium swallow examination showed carcinoma

TABLE XII

FOCUSED GRID TELECOBALT THERAPY
CLINICAL DATA—MISCELLANEOUS NEOPLASMS

No.	Unit No.	Age, Race, Sex	Type of Cancer	Stage	Total Dose at Hole Center	First Treatment Date	Died	Palliation Factor (P)	Survival Time (T) (mo.)	Palliative Index (P×T)*	Remarks
1	13-05-90 JC	54 NM	Carcinoma of prostate, bone metastases		4,800 r (incomplete)	7/ 9/57	9/ 7/57	0	2	0	Insufficient therapy to evaluate grid
2	A7-26-18 AB	70 WF	Adenocarcinoma of colon		12,000 r	10/22/57		1	14	14+	Lymph nodes dramatically regressed
3	14-59-55 LS	45 WF	Hodgkin's disease		12,000 r	1/13/58		3	12	36+	Patient returned with involvement of cervical spine; tracheal compression
4	14-59-46 AM	3½ WM	Wilms's tumor with lung metastases		12,000 r	1/20/58	4/22/58	0	3	0	
5	14-67-92 GM	57 WM	Carcinoma of pancreas, islet cell		12,000 r 12,000 r	3/11/58 6/11/58		2	9	18+	Large epigastric mass decreased in size; recurred but did not respond as well with second course of treatment; died 1/29/59
6	11-75-80 JT	74 NM	Liposarcoma of scrotum		12,000 r	6/16/58		3	6	18+	At most recent follow-up doing well; no residual mass
7	14-33-91 SD	55 WM	Lymphosarcoma		1,200 r 1,200 r (incomplete)	11/14/58 11/17/58		1	2	2+	Only 2 treatments; considerable improvement in one month's time; died 1/13/59

* See footnote to Table VIII.

of the upper third of the esophagus. Thoracotomy on July 10, 1957 revealed a carcinoma which involved the esophagus from the thoracic inlet to the azygos vein. The mediastinal and paravertebral lymph nodes were involved. Although the primary lesion was considered nonresectable, because of atelectasis of the right middle lobe, a lobectomy was performed. Microscopic examination showed poorly differentiated squamous cell carcinoma of the esophagus.

The patient was referred for therapy, and it was elected to attempt palliation by grid therapy. The following factors were used: Barnes-Keleket telecobalt apparatus; half value layer 12 mm. Pb; field size with grid 13×13 cm.; 50 cm. skin source distance. A superior anterior midline chest portal was employed. A dose of 1,200 r was given daily for a total of 12,000 r (July 31, 1957, to August 13, 1957). During the follow-up roentgenographic examinations, the esophagus showed remarkable improvement with the previously irregular, stenotic segment becoming smooth and patent (Fig. 3, *A* and *B*). The patient was able to swallow food, but the over-all clinical picture was not considered good and he died on October 25, 1957 (P-1, T-3, PI-3).

CASE III. TH 14-43-93 WM 65. *Epidermoid Carcinoma of the Left Maxillary Sinus.* The patient presented with a vague history of several months of swelling over the left cheek plus a bleeding sore below the right eye. Both of these areas had grown rapidly. Physical examination revealed a 3 cm. circular ulcerated lesion over the right temple with a 1 cm. elevation. This lesion bled freely. Grossly, the face was asymmetric, with the left cheek protruding 2 cm. further than the right. Inside the mouth, the entire left superior alveolar ridge was replaced by a 3×6×2 cm. elevated, granular, friable, easily bleeding lesion. Sinus roentgenograms revealed that tumor tissue had filled the entire left antrum, eroded the medial wall into the left nasal cavity, destroyed the floor of the left orbit, and dissolved and pushed out the anterior wall of the antrum so that several teeth were lying loose in the soft tissue. To prevent fatal hemorrhage, the left external carotid artery was ligated. Biopsy revealed poorly differentiated squamous cell carcinoma of the left antrum.

The patient's condition was considered completely hopeless. He was accepted reluctantly in order to attempt palliation of bleeding, pain, and tumor size. The following factors were used: Keleket-Barnes telecobalt apparatus; half value layer 12 mm. Pb.; field size with grid 13×13 cm.; 50 cm. skin source distance; 1,200 r as measured in air through a port centered over the left antrum was given daily. A total dose of

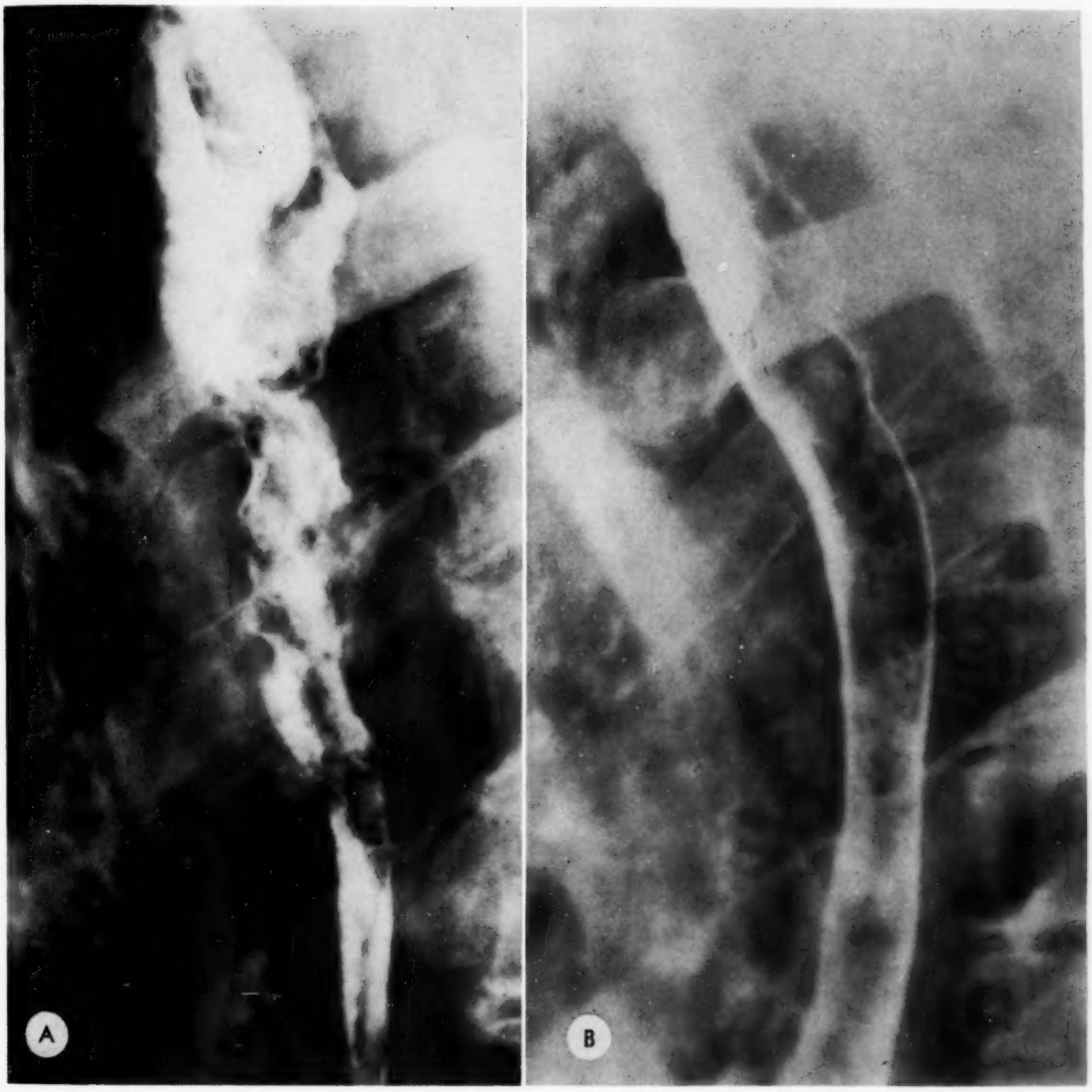

Fig. 3. Case II. Carcinoma of esophagus. (*A*) Pretreatment roentgenogram showing ragged tumor involving upper one-third of esophagus. (*B*) Post-treatment roentgenogram. Note smooth open lumen.

12,000 r was administered from December 10 to 24, 1957. Midway in the course of treatment, there was a noticeable decrease in the size of the cheek mass, and the patient had less pain and no bleeding.

Two months following completion of grid therapy, the patient returned with a symmetric face and no evidence of tumor involvement, by gross or by roentgenographic examination, in either the maxillary sinus or alveolar ridge.

Four months after treatment, the tumor was still not evident on the left side which had been treated. Roentgenograms demonstrated the left sinus to be essentially normal (Fig. 4, *A* and *B*). Physical examination and sinus roentgenograms revealed that the right antrum was now bulging with tumor. The patient suffered a cerebral vascular accident and, due to his inability to cooperate, the right side could not be treated. On May 7, 1958, the patient died in a nursing home (P-2, T-6, PI-12).

Case IV. RA 13-48-62. *Adenocarcinoma of the Cervix—Stage IV.* This thirty-seven year old Negro housewife was referred to the hospital because of intermenstrual bleeding and lower abdominal cramps. About eight months before admission, the patient first noted intermen-

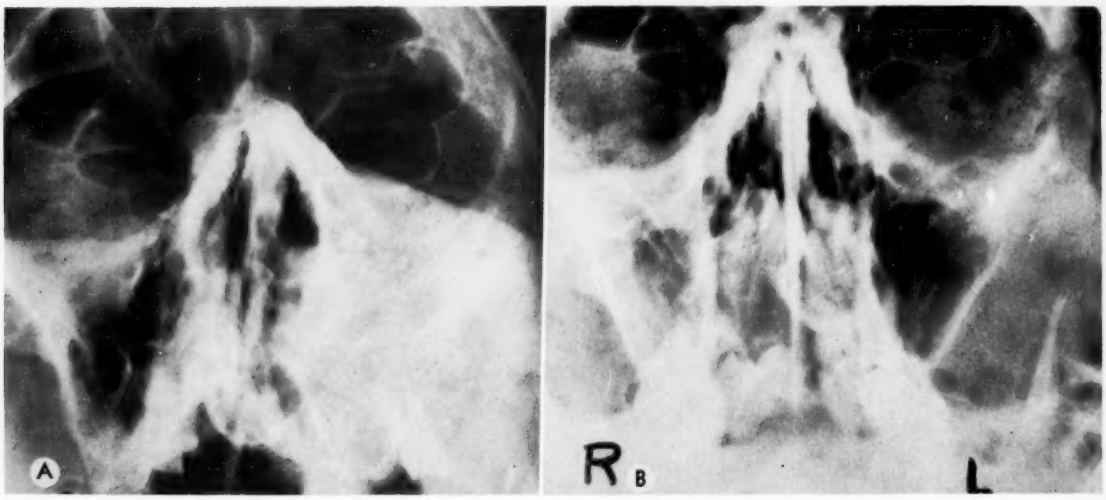

FIG. 4. Case III. Carcinoma of left maxillary sinus. (*A*) Roentgenogram showing pretreatment destruction. (*B*) Roentgenogram showing post-treatment improvement of left antrum.

strual spotting which was worse after intercourse. She had also developed a vaginal discharge. The patient said she had lost 20 pounds in weight and had increasing constipation.

Examination of the abdomen revealed a symmetric enlargement due to a hard, fixed, non-tender, fairly smooth mass arising out of the pelvis and extending to the umbilicus. Pelvic examination showed the cervix to be replaced by a friable, hard, necrotic mass of easily bleeding tissue. There was extension from the vesicovaginal septum to the introitus. The pelvis was filled with hard, fixed, non-tender masses and the adnexae were not identified. Rectal examination revealed marked narrowing and distortion $3\frac{1}{2}$ inches from the anus. Cystoscopic examination showed elevation and distortion of the bladder base, and sigmoidoscopic examination showed fixation and narrowing from a mass exerting extrinsic pressure on the right anterior wall of the rectum. The nonprotein nitrogen was 27 mg. per cent; hemoglobin was 6 gm. per cent and hematocrit 21.5. A biopsy revealed adenocarcinoma of the cervix.

The tumor conference considered surgery impossible and, although her condition was considered hopeless, the patient was accepted for grid radiation therapy. The following factors were used: Keleket-Barnes telecobalt unit, half value layer 12 mm. Pb; 50 cm. skin source distance ; a 13×13 cm. grid was applied to the left and right anterior pelvis in two fields. Each side of the pelvis was treated on successive days to a total of 12,000 r in air delivered between the dates of May 27, 1957 and July 3, 1957. In subsequent visits the patient still complained of lower abdominal discomfort, but her bladder and bowel functioned normally. There was no bleeding. Pelvic examination revealed a large crater which replaced the cervix and was seen to be connected with the abdominal mass. The abdominal mass still filled the pelvis and lower abdomen to the umbilicus. The parametrium was frozen. Palliation was considered negligible. The patient died on September 23, 1957 at home (P-0, T-4, PI-0).

CASE V. WM 14-44-70. *Carcinoma of the Lung.* This patient was a fifty-seven year old white man who came to the clinic on December 13, 1957 complaining of a chronic cough productive of purulent sputum for twenty years but aggravated in the past six months. During the last two months he had developed a precordial pain and smothering spells which he associated with his cough. The pain radiated to the shoulders. Anorexia, dysphagia, and a weight loss of 15 pounds were also noted. In recent weeks there had been some blood flecks in the sputum. This patient had been a heavy smoker—almost two packs a day since he was eighteen years of age.

Physical examination revealed a thin, slightly dyspneic white man who appeared chronically ill. Distention of the neck veins and veins of the arm and chest was noted, as well as enlargement of the lymph nodes in the right supraclavicular region. The trachea was de-

viated to the left. A chest roentgenogram revealed a mass in the right upper mediastinum 7 cm. in diameter involving the right hilus and probably the superior vena cava. Bronchoscopic examination showed compression of the trachea from a mass on the right side. Biopsy revealed chronic inflammation but no tumor. A thoracotomy on January 9, 1958 disclosed a large slightly nodular mass extending from the right hilus to the right superior mediastinum. The mass displaced the trachea to the left and infiltrated the thoracic inlet. The surgeon did not consider the obvious tumor tissue resectable. Microscopic examination revealed necrotic debris, strands of fibrous tissue, and atypical cells.

The patient was referred for grid telecobalt therapy and the following factors were used: Keleket-Barnes telecobalt apparatus; half value layer 12 mm. Pb; 50 cm. skin source distance; a grid portal 13×13 cm. was applied to the right anterior chest. From January 16 to 29, 1958, 1,200 r per day was given to a total of 12,000 r as measured in air in the hole center. In subsequent follow-up visits, although the mass had decreased in size as seen roentgenographically, and the obstruction of the superior vena cava had regressed, the patient was still considered to have negligible palliation because of dyspnea. He died on April 9, 1959 at home. No autopsy was obtained (P-0, T-2, PI-0).

Case VI. AP 15-95-68. *Squamous Cell Carcinoma of the Hard Palate.* The patient was a fifty-nine year old Negro woman who complained of swelling in the left jaw and pain of approximately five months' duration. She had been referred by her family doctor with a diagnosis of possible pterygoid abscess of the left jaw. Her health had been fair until June, 1958 (about six months before admission), when she noted a pain and tooth ache in the left upper jaw that became progressively worse. She had intermittent attacks of chills and fever. On physical examination her temperature was noted to be 102.6°F.; her breath was foul; and she appeared acutely ill. There was marked swelling and tenderness in the left upper jaw with a palpable mass extending deep into the subcutaneous tissues in the roof of the mouth. The mass was 8 cm. in size and extended to the zygomatic arch. Massive edema was noted on the left side of the face from the temple to the submaxillary area. There was associated tenderness, redness and heat. Inside the mouth the one remaining molar tooth was tender and there was a necrotic and fluctuant mass over the posterior alveolar margin, both medially and laterally. Incision and drainage were done and necrotic purulent material was found in a large cavity. Microscopic sections revealed poorly differentiated squamous cell carcinoma of the hard palate.

The patient was accepted for grid palliative therapy. The following factors were used: Keleket-Barnes telecobalt unit; half value layer 12 mm. Pb; 50 cm. skin source distance; a 13×13 cm. grid field was directed to the anterior left side of the face. Doses of 1,200 r per day were given from December 1 to 12, 1958, for a total of 12,000 r in air in the hole center. On subsequent follow-up visits, there was no regression in the size of the tumor or alleviation of pain. In fact, both the pain and size of the tumor increased. Repeat sinus roentgenograms showed further left maxillary sinus involvement and bone destruction. The patient died on April 29, 1959 at home. No autopsy was obtained (P-0, T-1, PI-0+).

CONSTRUCTION OF THE GRID

The grid used on these patients was constructed from a block of lead 10×10 cm. in area and 5.4 cm. thick (slightly less than 5 half value layer for Co^{60} radiation). Twenty-five holes 10 mm. in diameter are arranged in a square with 5 holes on each side. The holes are focused by diverging them toward the patient. The distance between hole centers on the source side is 16.3 mm. and on the patient side 19.3 mm. The ratio of lead area to hole area on the source side is 2.4:1 and the ratio of lead area to hole area on the patient side is 3.7:1.

DATA PERTINENT TO DOSIMETRY

The projected grid area at 50 cm. skin source distance is 13×13 cm. The distance between projected hole centers at 50 cm. skin source distance is 27.4 mm. With an open field intensity (cone #15) considered to be 100 per cent, the radiation intensity in the hole center at 4 mm. depth of the phantom is 85.3 per cent. At a 4 mm. phantom depth, the intensity in the hole center drops to 50 per cent at a radius of about 7 mm. around the hole center. The

ratio of the area with less than 50 per cent of maximum intensity to the area with more than 50 per cent is 3.9:1. The intensity in the peripheral holes compared to the holes in the center of the field drops off 10 per cent. The radiation between two adjacent holes of the lead block is 13 per cent of that in the hole center. The radiation between four holes is only 7 per cent of that in the center of the hole. At 4 mm. phantom depth, the ratio of mean intensity under the lead to that of the maximum in the hole center is 1:10. The same ratio at 19 cm. phantom depth is 1:2.9. The ratio of the volume dose with grid to the volume dose of an open field equals 1:3.3.

Our source originally had 1,100 curies and now has approximately 650 curies. The intensity of the radiation on the skin in the center of the hole is approximately 60 r per minute, and the time of delivery of a surface dose of 1,000 r is approximately sixteen minutes.

A study was made of the intensity distribution of radiation from one of the holes of the grid in the center of the field. By means of film dosimetry[5,7] exposed at various depths of a phantom, a family of symmetric distribution curves was obtained.[6]

A study of these curves showed that with increasing depth each succeeding curve becomes flatter. The curve shows a discrete grid pattern at superficial levels which becomes more homogeneous at deeper levels.

It was clinically important to check whether, with repetitive treatments with the grid, it was possible to obtain a good grid pattern distribution in the body. Accordingly, a film was placed underneath a patient and the grid was placed in the treatment position. One exposure was made and this film was used as a standard. The patient was moved and the grid was repositioned ten different times with the dosimetry film adherent to the exit port. It may be noted that the registration of the grid pattern on ten different positionings was remarkably close to the grid pattern produced with one exposure (Fig. 5).

BIOLOGIC EXPERIMENTS WITH GRID IRRADIATION OF MICE[4]

We attempted to find out the biologic significance of the grid irradiation by using it to kill mice and then comparing that dose with the dose required using the homogeneous beam. The 50 per cent lethal dose in 30 days time (LD 50/30) was about 700 r and the LD 50/30 for grid radiation was 1,800 r. The ratio of the grid LD 50/30 to the homogeneous beam was 2.5:1.

Judging from this biologic end point, the clinical doses may well have been too small. In future clinical experimentation with apparatus with a high rhm, a higher total dosage should be investigated.

The grid used in animal experiments was considerably finer than the clinical one. The ratio of the homogeneous volume dose to that of the grid was 2:1. There is a real possibility that a biologic sparing factor exists in favor of the grid, since a given volume grid dose equal to the homogeneous volume dose exerts a lesser biologic effect as indexed by the LD 50. For local irradiation, the sparing ratio may favor the grid even more.

DISCUSSION

In this series of 87 cases of cancer, the disease was so advanced that under ordinary circumstances the radiotherapist would not have accepted the patient for treatment. Conventional therapy has some disadvantages. The duration of treatment is long compared to the short life expectancy. Frequently there is aggravation of pain and suffering due to local reaction. There is also generalized malaise due to massive destruction of tumor cells as well as diminished viability of normal tissues. Occasionally, with conventional therapy, a paradoxical cure is obtained—the tumor tissue is destroyed but the anatomic and physiologic integrity of a vital organ is disturbed sufficiently to cause death.

In telecobalt grid therapy, it has been possible to deliver a relatively large dose of radiation within a period of ten treatment days. Many of the patients experienced relief of pain and hemorrhage and showed

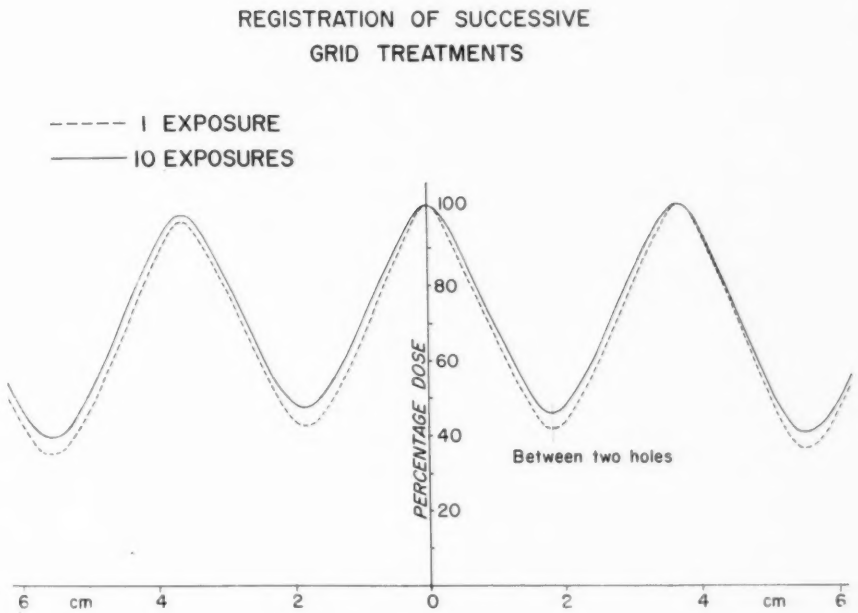

Fig. 5. A registration comparison of dose measurements during 1 exposure with those during 10 exposures by means of film dosimetry.

marked regression in tumor size. Some of the organs involved returned to a more normal function. This method of treatment contributed little or no discomfort to the patient during or after treatment. The advantages of this method have made it feasible to accept many more patients with advanced cancer. While it is probable that the longevity of the patient has not been improved to any great degree, the treatment has added considerably to his comfort.

The exact biologic mechanism of this mode of therapy is speculative. The nonhomogeneity of the grid radiation pattern may be analogous to a geometrically perfect radium implant (Fig. 6). It is well known that radium implants can give striking therapeutic results in the treatment of cancer.

The one feature that both the radium or cobalt implant and grid therapy have in common is a cyclical pattern of energy absorption in the tissue. Both methods have high gradients in the dose distribution.

It is rather remarkable that the measurement of the dose distribution in grid therapy is close to the calculated dose distribution of a needle implant. One calculation through the midplane of a needle implant yielded a ratio of approximately 1:5 when the area of more than 50 per cent of the maximal dose was compared with the area of less than 50 per cent of the maximal dose. The same ratio with grid therapy was approximately 1:4.

With grid therapy, the gradients are higher in the superficial structures and have a tendency to diminish in the deeper structures. The superficial tissues are thus spared to a greater degree than the deeper tissues. The grid pattern with telecobalt therapy is maintained at much greater depths in the tissue than with the conventional grid therapy. Preliminary data in animal experimentation indicate that there may be a biologic sparing factor which is in favor of the grid. It is not inconceivable that grid therapy may work by killing enough tumor cells to release sufficient antigens to elicit immune responses to cancer cells by adjacent normal cells and the immune mechanisms of the body. Pending biologic proof, it must be assumed that the grid telecobalt therapy increases the beneficial gradient between killing the

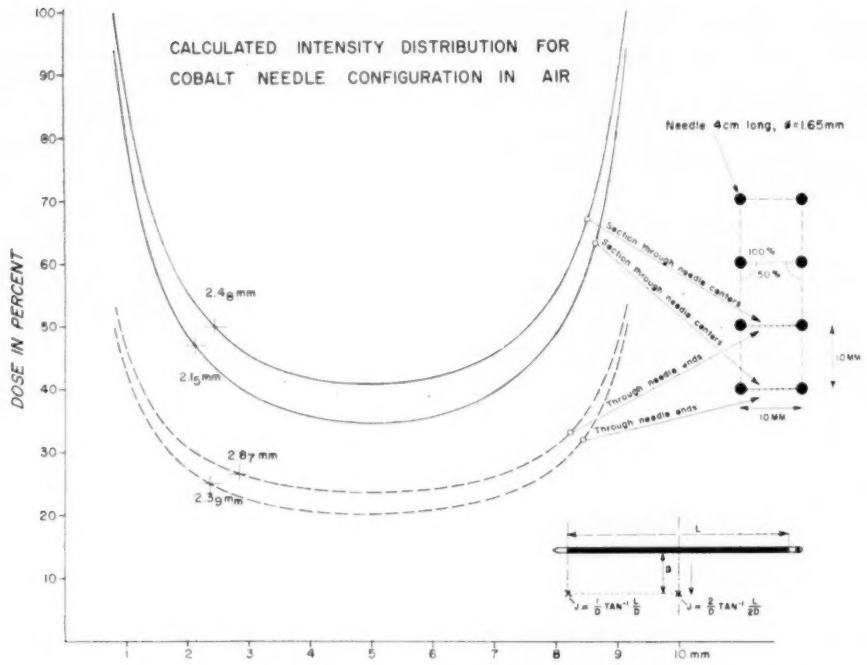

FIG. 6. An analogy can be drawn between radium needle implants and grid therapy. Note similarity of dose gradients of grid in Figure 5.

cancer cell and sparing the normal cell. It is agreed that some cancer cells do not receive much radiation and will remain viable. Even if neoplastic cells remain viable, the tumor bed and the humoral and cellular defense mechanisms may be so modified that the tumor becomes incapable of further growth and aggression.

SUMMARY

A series of 87 cases of advanced cancer was treated with focused telecobalt grid therapy. Fifty-one patients (59 per cent) experienced appreciable to striking palliation. No palliation was observed in 36 patients (41 per cent). The best palliation results were in patients with carcinoma of the bladder (78 per cent) and the least impressive in patients with carcinoma of the lung (36 per cent).

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VOL. 85, NO. 1

MOVING-BEAM THERAPY WITH COBALT 60: ITS ADAPTABILITY TO THE LESION SHAPE TO BE TREATED*

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THE concept of moving-beam therapy, either as arc therapy or as rotation therapy, was first brought forward and partly explored as early as 1914, and accounts of this type of therapy have appeared in the literature from time to time (*e.g.*, Dessauer *et al.*,[3] 1937; Flax,[5] 1937; Hawley,[8] 1940; Munson,[11] 1946). The wider practical application of the method, however, has only a few years' history (O'Connor,[12] 1956; Fowler and Farmer,[6] 1957; Morrison *et al.*,[10] 1957; Farmer,[4] Fowler,[7] Chance,[2] Snelling and Stern[13], 1958). This developed, initially, against the background of roentgen therapy pursued with what we now regard as relatively low, conventional roentgen-ray energies, ranging from 200–250 kv. Its purpose was primarily to improve upon the tumor dose values, relative to skin dose, that can be obtained by multiple-beam techniques with this type of radiation, especially for such deeply seated and approximately centrally situated sites as the esophagus.

It happened that while the methods of moving-beam therapy and the associated techniques for dose computation were becoming a practical possibility, supervoltage apparatus, using either roentgen-ray generators or, more simply, highly active radioisotope sources, were also becoming more readily available. It was probably inevitable, therefore, that moving-beam supervoltage equipment soon came into production (*e.g.*, Braestrup *et al.*,[1] 1953) and this possibly without much inquiry as to whether the marriage between the movement of the beam and the beam itself was a marriage only of convenience, or of real additional therapeutic value.

There is a school of thought that considers the use of a moving-beam unnecessary for supervoltage therapy with beams of cobalt 60 gamma radiation or roentgen rays generated at 2 million volts or more. This school considers that with this radiation it is possible, by means of ordinary, but well planned multibeam techniques, to deliver completely adequate tumor doses to all sites without undue skin reaction. It sees little point, therefore, in adding the possible complexities and certain extra expense that moving-beam apparatus entails.

We must admit that, until we had personal experience with moving-beam supervoltage therapy, we also subscribed somewhat to this school of thought, but we must add that our reservations about the additional value it might have were also influenced by other considerations of a very different character.

It had seemed to us that, unless it is properly used for the most suitable cases, moving-beam therapy (expecially simple rotation therapy) carries with it the danger of attempting to fit the patient (or rather his disease) to the apparatus. This would be contrary to all the progressive development that has occurred in radiotherapeutic physics, which emphasizes the fitting of the apparatus (or rather its beam) to the patient. We were thus obliged to question whether a moving-beam apparatus would be applicable, as such, to more than a minority of the patients treated with it. Indeed, this question, either deliberately, or subconsciously raised, is possibly behind the attempt that is made on much moving-beam equipment to provide facilities also for fixed beam therapy.

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FIG. 1. The theratron rotating Co^{60} unit.

After nearly two years of experience with moving-beam supervoltage therapy with a cobalt 60 beam, we now realize that, provided sufficient attention is given to the physical planning of individual patients, it is possible to achieve a very wide, controlled range of dose-contour patterns such that very many patients may be treated by this form of therapy with distinct clinical advantage. It is the chief purpose of this paper to describe and illustrate a series of techniques for treating a variety of disease sites of different areas and shapes, in order to demonstrate this point.

THE MOVING-BEAM APPARATUS

The apparatus we have used is a theratron containing 1,750 c of cobalt 60 originally and made by Atomic Energy of Canada, Ltd. This apparatus (Fig. 1) readily permits rotation and arc therapy as well as other more complex procedures that we have not used as yet.

METHODS OF DOSE AND DOSE CONTOUR COMPUTATION

For the computation of dose and of the dose contours that represent the total dose distribution throughout the treated tissues, due to any particular rotation or arcing technique, we have found it preferable to apply the methods developed by Jones and his colleagues.[9] Originally, one of the disadvantages of rotation and arcing techniques had appeared to be the complexity of computation of complete dose distributions. These workers, however, have made it clear that with Co^{60} gamma radiation, or other equivalent radiation, many of the expected difficulties do not arise.

At first our computations were based upon our own measured dose contours expressed in the usual way with the maximum ionization (at 0.5 cm. below the treated surface) taken as 100 per cent. Atomic Energy of Canada, Ltd. has since produced carefully measured dose contours, in which the dose at the center of rotation is expressed as 100 per cent. We now prefer to use the latter since these permit more accurate interpolation.

LOCALIZATION OF DISEASE SITE AND AREA TO BE TREATED

For the determination and evaluation of a technique for treating any particular area at a given site, the first requirement is a suitable, accurate, anatomic contour of the patient, reproduced on paper, with the area to be treated precisely marked within the contour.

In practice the anatomic contour is obtained by means of one or other pieces of apparatus which need not be described here. The methods used for localization of the treated area within the contour depend upon the actual site of the disease and include palpation and direct measurement, direct radiography with or without radiopaque markers introduced at known positions, cystography with the patient in the treatment position, etc.

DECISION UPON AND EVALUATION OF TREATMENT TECHNIQUE

The treatment technique used is determined and evaluated with reference to the contour obtained as above. Initially, this

was a rather slow and tedious process because several possible techniques had sometimes to be examined before the most desirable one was found. However, with experience and the accumulation of data that may be used repeatedly, it is now possible to arrive at a satisfactory technique relatively quickly.

The complete dose-contour system for any chosen technique is determined by means of the methods already referred to (Jones *et al.*,[9] 1956) and the daily dose, treatment time, etc., are specified in the light of these contours. It is our aim in producing a suitable technique, to include the area to be treated as accurately as possible within the 80 per cent dose contour, where 100 per cent is the maximum dose delivered within the treated area.

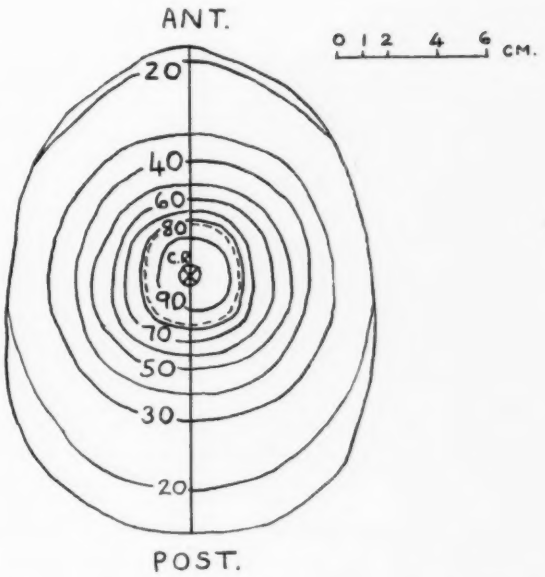

Fig. 2. Basic 360° rotation treatment of the uvula.

PRACTICAL REALIZATION OF PLANNED TREATMENT TECHNIQUE

That all patients are treated lying down and that the beam may easily be rotated into any position make the accurate realization of a desired moving-beam technique simpler than is the case with ordinary fixed beam techniques. The essential requirement, of course, is that the center of rotation of the beam be correctly positioned within the patient.

At the time of the first treatment of a given patient, by means of a specially designed bridge that fits temporarily onto the treatment couch and over the patient and using the beam-defining and beam-exit light indicators, a number of surface markings are made on the skin which enable one to position the patient correctly on this and future occasions. The whole of this procedure is greatly facilitated by the motorized movements of the couch which enable the patient to be moved very easily and quickly in any desired direction.

SOME EXAMPLES OF VARIOUS TECHNIQUES

1. *Treatment of Carcinoma of Uvula by Full 360° Rotation.* The field used was 4 cm. wide (×8 cm. long) at the center of rotation. Figure 2 shows the dose distribution obtained with full 360° rotation. This is a typical distribution for full rotation—almost circular dose contours and a rapid fall of dose with distance from the center of rotation. In this and the following illustrations the area to be treated is delineated by the broken line.

2. *Treatment of Carcinoma in the Nasopharynx Using One Rotation Center and Two Equal Arcs.* This case (Fig. 3) illustrates how the dose contours may be made oval in

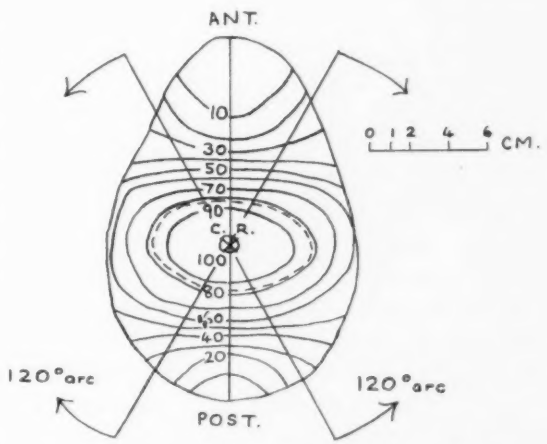

Fig. 3. One center equi-arc rotation cycling for treatment of the nasopharynx.

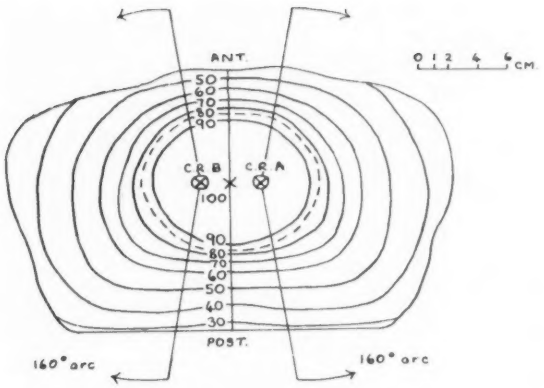

FIG. 4. Two center equi-arc rotation cycling for treatment of the bladder.

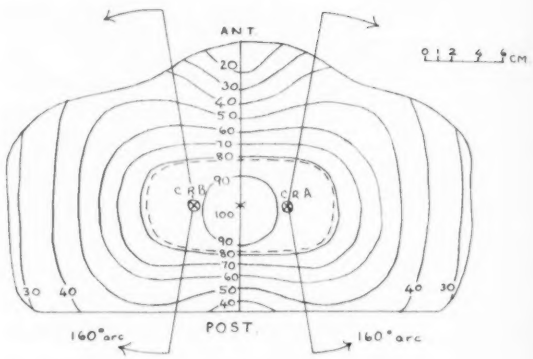

FIG. 5. Two center equi-arc rotation cycling for treatment of the cervix uteri.

shape for the treatment of a limited volume of that shape, lying within the head or neck. Two lateral arcs of rotation are used with one common center of arcing. Each arc is of 120°, the central anterior and posterior regions of 60°, each being omitted from the treatment. The dose distribution shown is for a field 6 cm. wide (and 8 cm. long) at the center of rotation.

3. *Treatment of Carcinoma of the Bladder and Carcinoma of the Cervix by Means of Two Equal Arcs about Two Different Centers.* This kind of technique is especially useful when a large and approximately oval area is to be treated within the pelvis.

Figure 4 illustrates its application to the treatment of the whole bladder, this customarily being the objective at Westminster Hospital in the radiation treatment of carcinoma of the bladder. The field size used in this case is 10 cm. wide (×12 cm. long) at the center of arcing. The fall-off of dose towards the rectum is fairly rapid and the bladder is covered very adequately.

Figure 5 shows the use of the same principle for treating carcinoma of the cervix so that tissue out to the pelvic wall is included in the (80 per cent dose level) treated area. The arcing centers are more widely separated than before in order that the required larger volume is encompassed satisfactorily. In this example, the field is 10 cm. wide (×15 cm. long) at the center of arcing.

This technique is being applied to a series of advanced cases as *the* method of treatment, no intracavitary radium therapy being used.

4. *Treatment of Extensive Carcinoma of Floor of the Mouth by Means of Two Unequal Arcs about Two Different Centers.* This case called for irradiation of an area of considerable magnitude and elongation which extended almost to the skin surface. It is of interest also because the latter feature would normally lead one to consider that little is to be gained by the use of moving beams.

Figure 6 shows the dose distribution actually obtained by the use of two different centers of arcing and two different

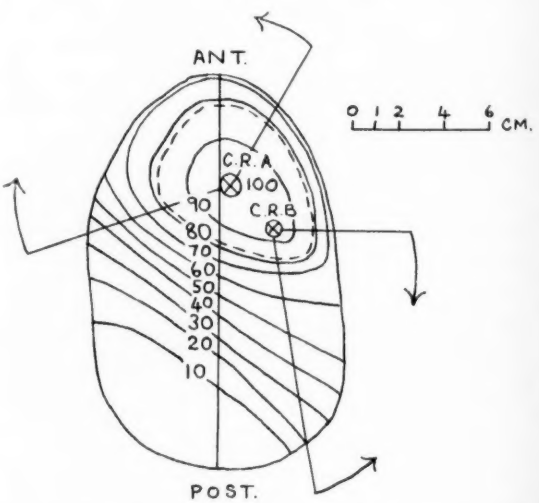

FIG. 6. Two center rotation cycling with two unequal arcs for treatment of an extensive area of the floor of mouth.

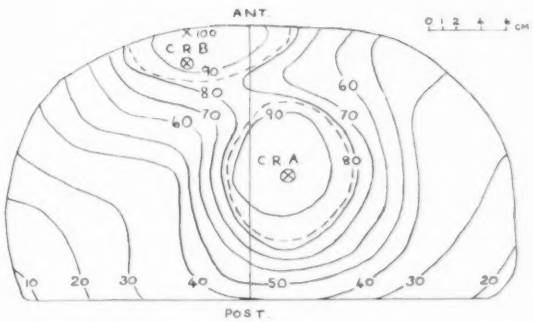

Fig. 7. Combined distribution for treatment of a recurrence in the vagina and a lymph node mass in the left groin (Figures 8 and 9 combined).

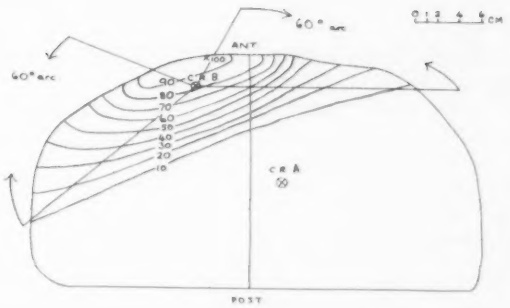

Fig. 9. One center equi-arc rotation cycling to treat the lymph node mass (see Fig. 7).

arcs. The field used was 6 cm. wide (×10 cm. long) at the arcing centers.

5. *An Attempt to Irradiate Two Separate Areas by Means of a Common Technique.* In this case of recurrent carcinoma of the vagina and a lymph node mass in the left groin, an attempt was made to devise a moving beam technique that would treat both these areas effectively.

The final dose distribution obtained is shown in Figure 7 where the two distinct zones of effective dose may be seen. This was achieved by what is really the summation of two separate techniques, each along the lines of those already described. Each of these uses two different arcs and one center of arcing and the dose distributions due to them separately are shown in Figures 8 and 9, in which the field sizes are 10 cm. in width (×15 cm. in length) and 6 cm. in width (×15 cm. in length), respectively, at the arcing centers.

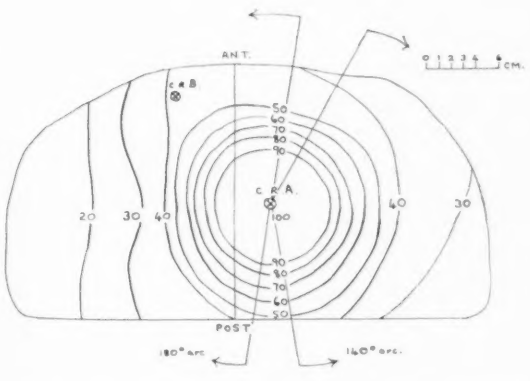

Fig. 8. One center rotation cycling with unequal arcs to treat the recurrence in the vagina (see Fig. 7).

GENERAL REMARKS

In all these techniques the emphasis has been upon the plane of rotation or arcing and the field used has been made sufficiently long to include the diseased tissue adequately in the direction perpendicular to this plane. Although we have not yet been able to pursue this aspect of the problem, it may be possible, by further elaboration of beam movement which the apparatus will in fact permit, to fit dose contours fairly closely to the disease in three dimensions.

SUMMARY

A series of moving beam techniques for treating a variety of disease sites of different areas and shapes, achieved by individual patient planning, is described. The very wide range of dose contour patterns which can be produced is arrived at by using multiple arcs and centers of rotation; thus a greater number of tumor sites may best be treated by a rotation technique than would first appear.

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We wish to acknowledge our indebtedness to Miss Nancy Legg, M.S.R.T., who carried out many of the computations necessary to determine the dose distributions we have shown.

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Vol. 85, No. 1

COBALT 60 TAGGED B_{12} AS A DIAGNOSTIC TOOL IN THE GENERAL ISOTOPE LABORATORY

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DURING the past seven years there have been many reports on the use of Co^{60} tagged B_{12} as a diagnostic tool.[2,3,5–8,10,12] It has been used by the gastroenterologist to evaluate intestinal tract absorption; the hematologist uses the study to evaluate hyperchromic anemias, and the neurologist and neurosurgeon use it when combined systemic disease is suspected. However, there have been no reports from a general isotope laboratory of its use in unselected cases. In presenting our material it is hoped that a clear-cut abnormal range can be identified. Also some of the pitfalls of the test will be pointed out for those planning to use it.

METHOD

All our studies were done by the urinary excretion method. The work of MacLean and Bloch[6] has shown this to be a valid technique. We have followed basically the Schilling procedure.[11] Our test meal contains 0.25 μg. of B_{12}, and this in turn contains 0.25 μc of Co^{60} radioactivity. Schilling originally used 2 μg. of B_{12} and 0.5 μc of Co^{60}.[11] Both of these test meals are in the physiologic range.[2,3,9] According to Glass and associates,[2,3] the absorption efficiency is best when the dose is under 2 μg. of vitamin B_{12}. The test meal was given only to patients fasting at least eight hours. No additional food was permitted until the 1,000 μg. flushing dose was given two hours later. Regular meals were then allowed. Barium does not alter the test.[1] All urine was collected over the next twenty-four hours and counted in 1,000 cc. aliquots and compared to a standard containing 20 per cent of the administered dose. Cobalt 58 B_{12} may have advantages but we have had no experience with it.[4]

MATERIAL

A total of 624 tests has been done. These patients have been referred to us by different services as shown in Figure 1. This is a reflection of interest and patient turnover on the respective services. It reflects a cross section of a general hospital.

RESULTS

The over-all results are shown in Figure 2. It will be noted that with the exception of the 2 per cent or less column, the results follow a uniform distribution curve. It logically follows that patients with an excretion rate of 2 per cent or under are abnormal. However, the 3 to 4 per cent group also deserves analysis. Of 36 patients in this latter group, 2 were felt to have pernicious anemia. No definite explanation or consistent diagnoses could be established in the others.

Of the 101 cases showing an excretion rate of 2 per cent or less, all were abnormal with the exceptions to be mentioned. Not all were checked with repeat studies and in-

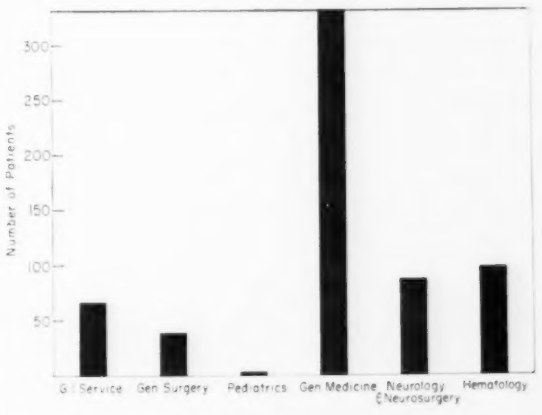

FIG. 1. Distribution of requests by various services Co^{60} B_{12} excretion test.

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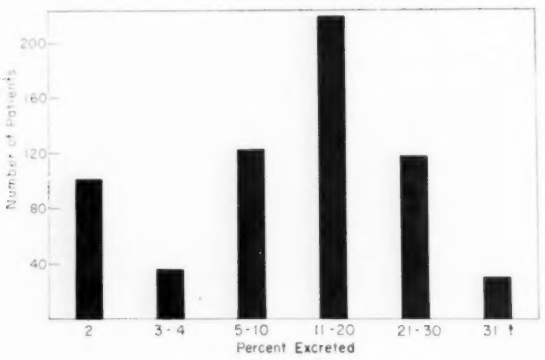

FIG. 2. Over-all results of Co^{60} B_{12} excretion test.

trinsic factor. One low test is sufficient for the diagnosis of pernicious anemia if this correlates with the clinical findings. Fifty-three of these cases were re-checked with intrinsic factor. The results are shown in Table I. Linitis plastica and total gastrectomy will produce results the same as pernicious anemia.[5] Three cases with questionable final diagnosis are listed in Table II. Cases 35 and 38 were listed in this group because we insist on the absence of free gastric hydrochloric acid for diagnosis of pernicious anemia. Case 22 may be pernicious anemia, but is so confusing we felt it should remain in this category.

The group subsequently proved normal also deserves comment. These cases occurred consecutively and aroused our interest. We felt that there existed some fault in the cobalt[60] tagged B_{12} supply. Repeat studies with a new shipment gave normal findings. Smith[13] has subsequently reported that radioactive B_{12} may be unstable.

Other sources of error include failure to give the flushing dose of nonradioactive B_{12} and an incomplete urine collection.[10] Food

TABLE I

RESULTS OF 53 CASES STUDIED WITH Co^{60} B_{12} AND INTRINSIC FACTOR

Pernicious Anemia	31
Malabsorption Syndrome	11
Linitis Plastica	2
Subsequently Proved Normal	6
Diagnosis Still Uncertain	3

TABLE II

CASES IN WHICH DIAGNOSIS WAS UNCERTAIN

Case 22	No anemia, no HCl, minor neurologic changes but also has diabetes and syphilis
Case 35	Neurologic consultation reported combined system disease but had free HCl
Case 38	Had free HCl, hyperchromic anemia and splenomegaly

or B_{12} ingestion within eight hours of the test will also alter the results.[1] If any of these factors are in doubt the test should be repeated.

SUMMARY

In the past there have been articles indicating that the excretion percentage of Co^{60} tagged B_{12} may be abnormal by as much as 13 per cent.[7] The distribution of results in our relatively large series would imply that only patients excreting 2 per cent or less are definitely abnormal. Those excreting 3 to 4 per cent are a border-line group which may be abnormal but usually is found to be normal, with some technical error occurring in the test. Certainly 5 per cent or above should be considered normal. The test is extremely valuable in the evaluation of patients with neurologic, hematologic and obscure gastrointestinal disease.

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INTRACAVITARY RADIOGOLD THERAPY*

A CRITICAL APPRAISAL OF ITS VALUE

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A COLLOIDAL solution of radioactive gold was successfully prepared and used in animal experiments by Hahn and co-workers[12] and employed in the treatment of malignant effusions in serous cavities in human patients by Muller[17,18] in 1947. Many reports have since appeared in the literature.[1,3,4,7,9,10,14,15,16,19,21,22,23,25] It is agreed that intracavitary radiogold therapy is not a curative treatment of cancer, but merely a palliative measure primarily for the reduction of fluid formation due to carcinomatosis, and that its usefulness is limited to carefully selected cases. Rather rigid criteria for the selection of patients have been advocated.[1,4,10,19,21] These, however, have seldom been heeded and various authors have lamented that their results could have been better had they selected their cases more strictly.[3,9,10,16,19,23,25] It would seem of considerable importance to know why this is so and how the therapeutic results may be affected. This information is sought in the following analysis of our series of 43 patients which is presented with other pertinent observations worthy of comment.

CLINICAL DATA

A total of 43 patients received intracavitary radiogold therapy: 17 for pleural effusion; 20 for ascites; and 6 for preventive treatment following discovery of peritoneal implants or spillage of cystic tumor content at laparotomy.

The sites and incidence of primary tumors in patients with pleural effusion are listed in Table I; those in patients with ascites in Table II. All of the 6 patients receiving preventive treatment had ovarian carcinomas.

The diagnosis in each patient was established by histologic examination of either the fluid or the tissue removed at operation or by biopsy or both. The importance of pathologic diagnosis has been emphasized by all workers because: (a) benign effusions may occur in cancer patients with associated cardiac, renal, hepatic, or nutritional diseases; and (b) benign effusions do not respond to radiogold treatment as a rule.[15,16,19]

TABLE I

PRIMARY TUMORS IN PATIENTS WITH PLEURAL EFFUSION

Site of Primary Tumor	No. of Patients
Lung	7
Breast	4
Ovary	3
Unknown	2
Pleura	1
Total	17

INDICATIONS AND CONTRAINDICATIONS

We believe that the criteria of Andrews *et al.*[2] are reasonable and realistic indications for intracavitary radiogold therapy. These may be summarized as follows: (1)

TABLE II

PRIMARY TUMORS IN PATIENTS WITH ASCITES

Site of Primary Tumor	No. of Patients
Ovary	7
Unknown	4
Appendix	3
Stomach	2
Uterus	2
Colon	1
Prostate	1
Total	20

* From The Department of Radiology, Baylor University College of Medicine and Jefferson Davis Hospital, Houston, Texas.

absence of symptoms due to neoplasm other than those related to effusion; (2) duration of effusion for several months before treatment; (3) absence of masses or lesions palpable or visible by roentgen-ray examination; and (4) absence of severe anemia and malnutrition.

Our experience indicates that these criteria have not been followed in many instances, with the predictable result of many failures.

SELECTION OF PATIENTS

Inasmuch as the Isotope Service sees only referred patients, the referring physicians of various clinical departments have the opportunity of preliminary selection of patients for radiogold treatment. In this respect, our experience indicates that, with a few exceptions, the referring physicians fall into two groups. There are those who refer all patients with effusion and those who refer none at all. It is our impression that the latter group may not know of or does not believe in this form of therapy. As a consequence of nonreferral, a number of patients suitable for radiogold therapy are denied the possible benefit without a consultation. The former group may honestly believe in the usefulness of radiogold therapy under *all* circumstances or, not infrequently, may just want to have everything possible done for their patients.

Of the referred patients, the final responsibility of selection rests with the isotope therapist. The decision with regard to indication for radiogold therapy should be based upon careful evaluation of the total picture of the patient: his disease, his symptomatology, and his prognosis. Good judgment depends upon absolute objectivity as well as sound experience. However, the isotope therapist may be pressed and tempted to give treatment even though the indication may not be clear in his better judgment. Treatment may be urged by the referring physician pleading for something to be done and arguing that nothing can be lost. Occasionally, the patient's family may express the desire for radiogold therapy. Consequently, some patients receive radiogold therapy when little or no palliation could be expected.

METHOD OF ADMINISTRATION AND DIAGNOSTIC SCAN

A number of methods and equipment for the administration of radiogold have been advocated.[6,8,11,13,24] We have adopted the simplest. The body cavity involved is tapped with a special 13 gauge trocar; as much fluid as possible is removed. A thin polyethylene tubing is threaded into the body cavity through the trocar, which is then withdrawn. By gravity displacement, the radiogold solution is flushed through the polyethylene tubing into the body cavity with a small volume of sterile normal saline solution.

Before the therapeutic dose of radiogold is delivered, a tracer amount (1–5 mc) may be given and a preliminary scintiscan is made after adequate distribution has been obtained. The polyethylene catheter is retained while the scan is being made.

This procedure is especially useful in cases where loculation is suspected. If the preliminary scan shows undesirable distribution or loculation, the therapeutic dose may be reduced or the treatment cancelled.

If the scan shows satisfactory distribution of the tracer dose (Fig. 1, *A* and *B*), the full amount of the therapeutic dose may then be given through the retained catheter. The puncture wound seldom requires suturing. A colloidin seal and a tight dressing are usually sufficient in preventing leakage.

DOSAGE AND TREATMENT SCHEDULE

The average single dose of radiogold given to our patients was 75 mc for pleural effusion and 150 mc for ascites.

A number of patients received more than one treatment. The reasons for multiple treatments are: (1) fractionation, (2) involvement of multiple cavities, and (3) retreatment. Our data are summarized in Table III. The number of cases is too small to warrant further discussion.

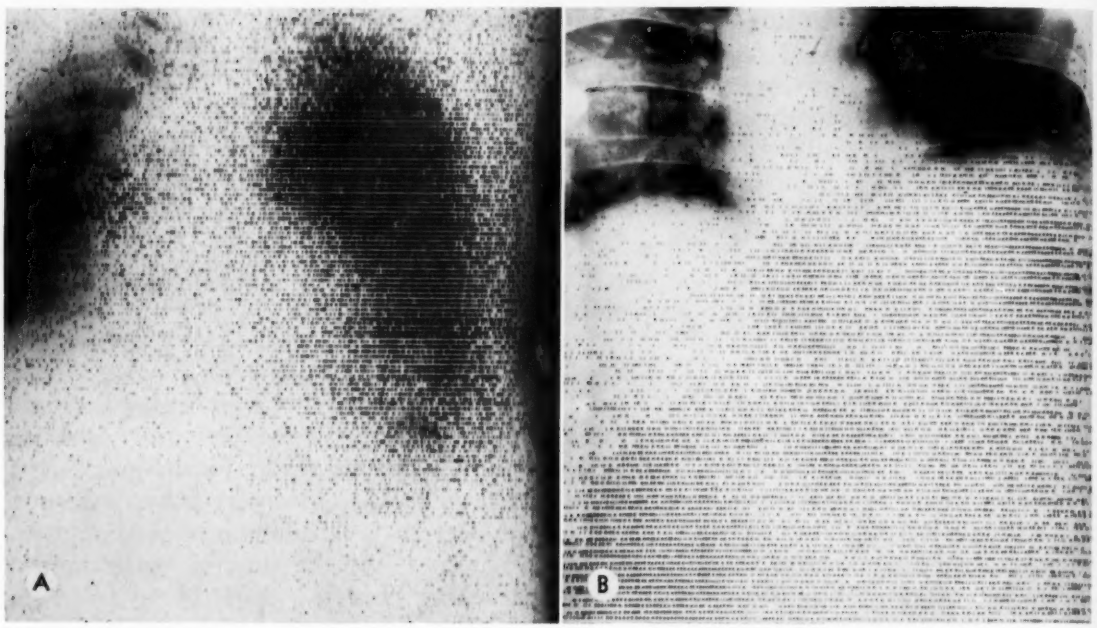

FIG. 1. Photoscintiscans of chest and abdomen following intracavitary radiogold injection. (*A*) Chest scan of a patient with inoperable mesothelioma and pleural effusion made after a tracer dose of radiogold showing satisfactory distribution. Note left cardiac border and mediastinal displacement. (*B*) Abdominal scan of a patient with ovarian carcinomatosis and ascites showing satisfactory distribution of radiogold. Note outline of liver.

RESULTS AND COMMENTS

It is recognized that the administration of 50–250 mc of radioactive gold into a pleural or peritoneal cavity with malignant effusion has no curative effect on the malignant disease. Its only palliative effect is the reduction or stoppage of fluid formation, and this is the sole objective of the treatment.

On this score, the results of therapy are rated as excellent, equivocal, or nil. Excellent result denotes marked reduction of fluid formation requiring, at most, one or no more tapping in patients surviving three months or longer. Equivocal result denotes patients surviving less than two to three months with only dubious change in the rate of fluid accumulation. Nil result denotes patients surviving less than one month with little or no change in the rate of fluid formation. Table IV shows the results in our cases. The figures are in accord with those reported in the literature. The high percentage of patients receiving doubtful or no benefit is largely attributable to the brevity of survival. Thus 9 of 17 patients with pleural effusion and 10 of 20 patients with ascites were dead within two months after the administration of radiogold (Table V). These early deaths were attributable primarily to the advanced stage of cancer. The clinical picture of cachexia, anemia, pain, etc., should have contraindicated radiogold therapy. If these cases had been excluded by proper selection, the figures would have shown 4 of 8 patients with pleural effusion and 6 of 10 patients with ascites demonstrating excellent response to radiogold treatment.

Further scrutiny of our data reveals that almost all of the patients with effusion of acute onset, short duration and rapid reaccumulation were dead within three weeks after the radiogold injection (Table VI). The uselessness of giving treatment to these patients at all is brought sharply into focus.

The data on the presence or absence of

TABLE III

SUMMARY OF MULTIPLE INTRACAVITARY INJECTIONS OF Au^{198}

Reason for Multiple Treatment	Case No.	Primary Tumor Site	Effusion	Dose and Schedule					Results
				1 (mc)	2 (mc)	3 (mc)	Total (mc)	Interval	
Fractionation	1	Ovary	Ascites	74	50	50	174	Weekly	Excellent
	2	Ovary	Ascites	50	50	74	174	Weekly	Nil
	1	Ovary	Pleural	34	94	60	188	Weekly	Excellent
Multiple Effusion	1	Ovary	Ascites	74	50	50	174	Weekly	Excellent
			Pleural	34	94	60	188	Weekly	Excellent
	3	Ovary	Pleural (right)	50	50	50	150	2 weeks	Excellent
			Pleural (left)	50			50	2 months	Excellent
Repeated Treatment	4	Ovary	Ascites	60	78		138	6 months	Excellent
	5	Ovary	Ascites	100	150		250	4 months	Excellent
	6	Stomach	Ascites	100	150		250	9 months	Excellent
	7	Appendix	Ascites	70	78	100	248	5 months 6 months	Nil
	8	Unknown	Ascites	40	70		110	1 month	Nil
	9	Breast	Pleural	50	60		110	30 months	Excellent
	10	Breast	Pleural	50	47		97	1 month	Nil
	11	Lung	Pleural	43	30	17	90	2 months 1 month	Nil
	12	Lung	Pleural	75	95		170	12 months	Excellent
	13	Pleura	Pleural	90	93	75	258	4 months 10 months	Equivocal
	14	Unknown	Pleural	75	75		150	1 month	Nil

demonstrable tumor mass in the peritoneal cavity in 20 patients with ascites are summarized in Table VII. Seven of 10 patients with demonstrable mass were dead within 2 months while 4 lived 3–12 months. Of 9 patients without demonstrable mass, 3 died within 2 months; 3 survived 13–16 months; and 3 are still living without ascites after radiogold therapy.

Of the 17 patients who have died of peritoneal carcinomatosis, 4 had received radium and/or roentgen-ray irradiation of the pelvis and 13 had not. Of the untreated group, 10 were dead within 2 months, while all 4 of the treated group lived considerably longer (Table VIII). It is interesting to note that the radiotherapists wisely withheld radiation therapy from the 13 patients because of the gravity of their condition.

While 4 cases is too small a number to warrant any conclusion, it would appear that radiotherapy may have retarded the growth of the primary tumor and contributed to the longer survival of the 4 treated patients;[4,10] and the prolonged survival provided a chance for radiogold treatment to be worthwhile. Muller's[17] superior results seem attributable to combined

TABLE IV

SUMMARY OF RESULTS OF Au^{198} THERAPY

Results	Pleural Effusion		Ascites	
	No. of Patients	Per Cent	No. of Patients	Per Cent
Nil	6	35	10	50
Equivocal	7	41	4	20
Excellent	4	24	6	30

TABLE V

CORRELATION BETWEEN SURVIVAL TIME AND RESULTS OF INTRACAVITARY Au^{198} THERAPY

Survival Time (mo.)	Results		
	Excellent	Equivocal	Nil
17 Patients with Pleural Effusion			
2 or less	0	3	6
3–6	0	3	0
6 or more	4	1	0
20 Patients with Ascites			
2 or less	0	0	10
3–6	1	2	0
6 or more	5	2	0

therapy in a great majority of his patients.

The data on the 6 patients who received preventive radiogold treatment for peritoneal implants or spillage of ovarian tumor are summarized in Table IX. We entertain the same hopes as for the preceding group but feel, like most authors, that the results are difficult to evaluate.

DISCUSSION

When our results are examined, it becomes clear that intracavitary radiogold therapy has been used in many patients in whom its indication was doubtful or negative.

TABLE VI

SUMMARY OF PATIENTS WITH ACUTE EFFUSIONS

Primary Tumor Site	Duration of Effusion (wk.)	Tapping Interval (da.)	Survival Time after Au^{198} (da.)
5 Patients with Pleural Effusion			
Pancreas	1	1– 2	11
Lung	9	3– 4	106
Lung	4	7–10	20
Ovary	1	1– 2	20
Unknown	3	3– 4	4
4 Patients with Ascites			
Ovary	3	1– 2	11
Uterus	2	3– 4	10
Prostate	6	7–10	20
Unknown	3	2– 3	2

TABLE VII

SURVIVAL TIME OF PATIENTS WITH ASCITES WITH OR WITHOUT DEMONSTRABLE MASS

Survival Time (mo.)	Demonstrable Mass	
	Present	Absent
2 or less	7	3
3–12	4	0
13–16	0	3
Still alive	0	3

It is apparent that there must be a reasonable life expectancy of three months or longer for radiogold therapy to be of any real palliative value to the patient, for it may take several weeks for the therapeutic effect to be realized.[4,16]

Rapid accumulation of fluid requiring thoracentesis or paracentesis every ten days or less is, in our experience, a very grave sign of relentless progress of the underlying malignancy. Radiogold treatment in such cases is useless. These observations are in agreement with those of Andrews *et al.*[2]

The presence or absence of a demonstrable mass as a criterion against or for radiogold therapy seems less firmly established by our data. Here again, the life expectancy and general condition of the patient are more important factors than tumor mass *per se*. The patient with or without demonstrable mass should, therefore, be individually evaluated with regard to the suitability of radiogold therapy on the basis of other clinical findings.

TABLE VIII

SURVIVAL TIME OF PATIENTS WITH ASCITES WITH OR WITHOUT RADIOTHERAPY TO PELVIS

Survival Time (mo.)	Pelvic Radiotherapy	
	Yes	No
Less than 2	0	10
Up to 11	0	3
Up to 17	4	0

TABLE IX

SUMMARY OF CASES RECEIVING PREVENTIVE INTRAPERITONEAL Au^{198} THERAPY

Age	Primary Tumor Site	Reason for Treatment	Dose of Au^{198} (mc)	Follow-Up		
				Year	Status	Ascites
66	Ovary	Peritoneal implants	75	5	Living	0
48	Ovary	Peritoneal implants	43	2	Dead	0
37	Ovary	Peritoneal implants and spillage	100	1	Living	0
44	Ovary	Peritoneal implants	110	¼	Dead	0
35	Ovary	Rupture of papillary cyst (adenocarcinoma)	70	2	Living	0
49	Ovary	? Spillage on removal of cyst (adenocarcinoma)	60	1	Living	0

The conditions governing palliation, in so far as radiation therapy is concerned, have been discussed by Paterson.[20] Two of the points he made are very pertinent here: (1) there must be reasonable expectation of relief; and (2) beyond a certain stage of decline, no palliation is possible. He wrote, "In the moderately advanced stages of disease, we can still do much to ease distress, but later when the patient has really begun to go downhill, is already febrile or cachectic and looks 'ill,' treatment is not a kindness and may even help to precipitate the end." With this view the laity concurs.[5]

It may also be mentioned that intracavitary radiogold treatment is an expensive procedure, averaging about $250.00 or more (Table x) per application.

SUMMARY AND CONCLUSIONS

1. Seventeen patients with pleural effusion, 20 patients with ascites and 6 patients with peritoneal implants received radiogold intracavitary therapy.

2. Nine of 17 patients with pleural effusion and 10 of 20 patients with ascites were dead within two months of treatment. In retrospect, these patients could not be expected to benefit from the radiogold therapy, the indication was doubtful or negative and the treatment results unsatisfactory.

3. Excluding the early deaths, the results of radiogold therapy were excellent in 4 of 8 patients with pleural effusion and 6 of 10 patients with ascites.

4. The factors and circumstances leading to unsatisfactory results are discussed. The importance of strict adherence to certain criteria for the selection of patients is emphasized.

5. Rapid accumulation and short duration of fluid formation were grave signs of relentless progress of the disease. They were observed in 5 patients with pleural effusions and 4 patients with ascites, all except 1 were dead within twenty days of radiogold treatment.

6. The presence or absence of mass *per se* is not a reliable criterion for the selection of patients.

7. It is the task of the isotope therapist to evaluate the total picture of the patient as a basis for his decision to give or to withhold treatment.

TABLE X

EXPENSE OF Au^{198} THERAPY

Average dose of Au^{198} (100 mc)	$ 50.00
Average stay in hospital (5 days)	100.00
Professional fee	$ 50.00– 100.00
Miscellaneous expenses	50.00
Total	$250.00–$300.00

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VOL. 85, NO. 1

THE DIAGNOSTIC AND PROGNOSTIC VALUE OF ORAL SMEARS IN THE RADIOTHERAPY OF CARCINOMA OF THE ORAL CAVITY AND OROPHARYNX

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THE radiosensitivity of benign and malignant cells from carcinomas of the cervix uteri has been evaluated in tissue sections,[3,13] and in vaginal or cervical smears.[4–6] There has been a paucity of reports concerning similar studies of oral carcinomas, although Hall and Friedman[7] found that valuable prognostic information could be obtained by a single biopsy during the second week of irradiation of carcinomas involving the oral cavity and oropharynx. The cytologic effects of radiation on benign and malignant cells in oral smears have been described, and preliminary prognostic implications postulated on the basis of observations on a small series of patients.[9–12] This report concerns the evaluation of the diagnostic and prognostic significance of oral smears in a larger series of patients who received external irradiation for carcinomas of the oral cavity or oropharynx.

MATERIAL AND METHODS

Direct smears were obtained from the surfaces of 55 oral carcinomas (tongue, gingiva, floor of the mouth, anterior tonsillar pillar, retromolar area, and hard palate) prior to, during, and after irradiation. Companion smears were taken from the adjacent uninvolved mucosa within the field of irradiation. The smears were taken with small wooden spatulas, since metallic instruments either slipped over the mucosa without removing sufficient material, or produced bleeding if pressure was increased. Cotton-tipped applicators were found to be the least desirable, since the secretions were absorbed into the cotton. The smears were fixed immediately in ether-alcohol and stained according to the standard Papanicolaou technique.[8] In most instances the examinations were done daily or tri-weekly during treatment and monthly following completion of radiotherapy. The following studies were made:

1. *Radiation changes in benign squamous cells.* A minimum of 100 benign squamous cells was examined in each smear, and percentage determinations of the following cytologic features of radiation change were made: (a) enlargement of cell diameter above 75 μ; (b) enlargment of diameter of the nucleus above 14 μ; (c) vacuolization of cytoplasm; and (d) multinucleation.

2. *Radiation changes in malignant cells.* (a) Maturation of cells. This was determined by two indices of maturation; the nucleocytoplasmic ratio and the degree of cornification. The former was determined by separating the malignant cells into well-differentiated and poorly differentiated cells on the basis of their relative cell and nuclear diameters. If the diameter of the nucleus exceeded one-half that of the cell, the cell was classified as poorly differentiated; less than one-half, well-differentiated. The percentages of cornified and noncornified cells were readily determined, since the cytoplasm of the former stains intensely red or orange with the Papanicolaou stain, while the cytoplasm of the noncornified cells is cyanophilic. (b) Retrogressive changes. The percentages of Caspersson's type A and type B cells were determined.[2] About one-half of the patients

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had smears which were too hypocellular to make accurate determinations of the nucleoprotein patterns. (c) Ultraviolet microscopic studies of nucleic acids. The smears of 11 patients were stained with acridine-orange and examined with the ultraviolet microscope, using blue-violet light according to the technique of von Bertalanffy and his associates.[1] The same smears were decolorized and then restained by the routine Papanicolaou technique.

3. *Exfoliation of malignant cells.* The number of malignant cells per 100 benign squamous cells was determined.

4. *Conversion of positive to negative smears.* The date of the last positive smear during or following treatment was recorded. Emphasis was placed on the presence or absence of malignant cells at the end of treatment, during the immediate post-treatment phase (one to three months), and at the time of follow-up visits.

5. *Detection of recurrent neoplasm.*

RESULTS AND DISCUSSION

RADIATION CHANGES IN BENIGN SQUAMOUS CELLS

Although cell or nuclear enlargement, and cytoplasmic vacuolization or multinucleation are not pathognomonic of radiation effect, the quantitative transformations during treatment were striking.[9,10] Enlargement of the cells was the earliest, most prominent, and most consistent alteration. Cells which exceeded 75 μ in diameter were infrequent in pretreatment smears, while during therapy a majority of the cells showed some enlargement, often several times their pretreatment size, 35–50 μ. Increase in nuclear size was less frequent, probably because of the large number of superficial cornified cells with nonreacting pyknotic nuclei. Multinucleation appeared later, and the multinucleated cells rarely had more than two nuclei, in contrast to multinucleated malignant cells which often had many nuclei. Vacuolization of cytoplasm varied qualitatively and quantitatively from case to case more than any of the other changes and showed less

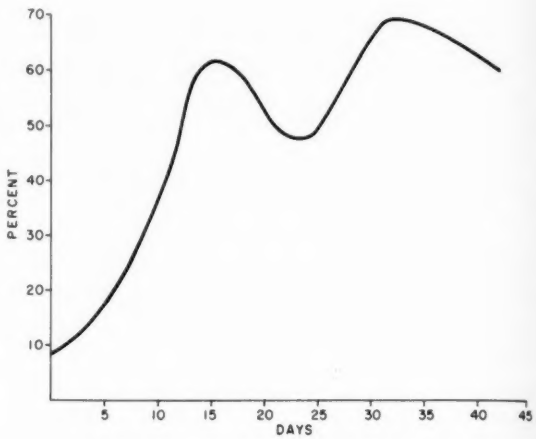

FIG. 1. Median percentage values of radiation change in benign squamous cells during treatment (55 patients).

constant sequential patterns in individual cases.

Cytoplasmic inclusions of bacteria, leukocytes, and granules exhibited no correlation with duration of treatment, or with any of the above alterations, for which reason they were not included in the results.

Recognizable cytologic changes were usually distinct by the fifth to seventh day, and these observations were supported by quantitative analyses (Fig. 1). There were considerable differences in the cytologic responses in different patients, but the chronologic patterns in individual cases were remarkably uniform, supporting the validity of the daily counts. Most patients exhibited a diphasic pattern, there being a median peak at the end of the second week of treatment, and a slightly higher second peak between the thirtieth and thirty-fifth days. A smaller number of patients had patterns with a gradual step-like increase. The depression between the two peaks of maximum response in the diphasic curves may represent persistence of unresponsive cells following removal of more radiosensitive cells, a temporary phase of cellular insensitivity, an interval between two different modes of physical or chemical action, or a pause between the direct and indirect effects of radiation.[10]

Clinical manifestations of radiation effect, such as "mucositis" or membrane formation, were seen between the time of onset of cytologic radiation change and the point of maximum development of these alterations, while tumor regression was usually observed at the peak of cytologic change.

No constant correlation could be demonstrated between the radiation changes in benign cells and the exfoliation or rate of disappearance of the malignant cells, the maturation or nucleoprotein patterns of the malignant cells, or the development of radionecrosis.

Preliminary observations[9,10] had suggested a direct relationship between the radiation response in the benign cells and the radiotherapeutic control of the primary neoplasm. The present studies, with a larger number of patients and longer follow-up studies, have demonstrated less convincing correlation. The median cytologic changes were only slightly greater in patients whose primary neoplasms were controlled, and, although the data may show valid general statistical differences, they are not sufficiently precise to permit practical prognostication in individual patients, especially in comparison with the correlation between the size of the primary tumor and its therapeutic control (Table 1). However, it was observed that the smears from each of the 4 patients who had uncontrolled *small* primary neoplasms (diameter of 2.5 cm. or less) exhibited poor cytologic radiation response, while the few patients without recurrence of large neoplasms at the end of twelve months or more showed vigorous cytologic responses.

TABLE I

RELATIONSHIP BETWEEN THE SIZE OF NEOPLASMS OF THE MOUTH OR OROPHARYNX AND PROGNOSIS

Clinical Status	Small (2.5 cm. or less in diameter)	Medium (2.5–3.5 cm. in diameter)	Large (over 3.5 cm. in diameter)
Total patients	19	7	25
Well	13	3	4
Residual neoplasm	4	1	16
Metastases	3	4	12
Dead	2	2	12

The characteristic "SR" cells described by Graham[4] in patients who had favorable radiotherapeutic results were rarely encountered, probably because such cells come from deep layers of the stratified squamous epithelium, and oral smears failed to disclose cells from these layers.

RADIATION CHANGES IN MALIGNANT CELLS

The radiation changes of the type described in benign cells were also demonstrated in malignant cells[12] but were more difficult to assess quantitatively because of the smaller number of cells and the frequent presence of similar alterations in non-irradiated cells. Attempts to measure these characteristics, therefore, were abandoned early in the study, and effort was directed instead to measuring the effects on maturation or differentiation of the tumors, and on Caspersson's criteria of variability.

Maturation, as determined by the nucleo-cytoplasmic and the cornification indices, was striking in only a few cases and showed no statistically valid correlation with clinical observations.

Caspersson and Santesson,[2] using ultraviolet spectrophotometric observations, found that the neoplastic cells in the growing and infiltrating, or perivascular portions of epithelial cancers were characterized by nuclei with abundant desoxyribonucleic acid (and chromatin). These were designated as type A cells in contrast to the type B cells which were found in the central, less viable areas of the neoplasm. The latter cells were regarded as prenecrotic, or at least less viable cells, and had nuclei which were larger, relatively poor in DNA, and rich in nucleolar ribonucleic acid (RNA). A preliminary study of 21 patients with oral carcinoma strongly suggested that these nucleoprotein patterns could be utilized to measure radiation ef-

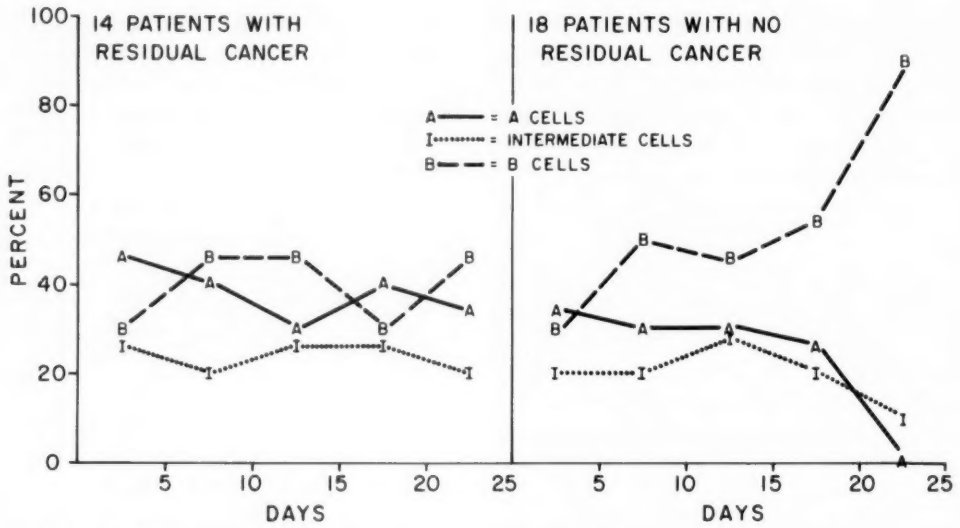

FIG. 2. Median percentages of Caspersson's type A and type B cells during irradiation.

fect in smears stained by the routine Papanicolaou method, and that there was a good correlation between the conversion of type A to type B cells and the results of radiation.[11] This line of endeavor has been amplified to include 11 additional cases, to investigate the additional follow-up of the original 21 cases, and to study the smears from another group of 11 oral cancers by ultraviolet microscopy using the fluorochrome, acridine-orange.

The findings of the current studies support our initial observations, namely, that the conversion from type A to type B cells is a good prognostic sign. As indicated in Figure 2, the median percentages of type A cells decreased only slightly in 14 patients who had residual carcinoma, while there was a pronounced decrease of type A cells and a proportionate increase in type B cells in the 18 patients with no clinical evidence of residual neoplasm. The contrast became most marked between the fifteenth and twenty-fifth days, although in some instances the critical measurements had to be made prior to this time because of the sparsity of malignant cells by the fifteenth day of treatment. In addition, the patients with good clinical radiation effect originally had fewer type A cells.

Unfortunately, these determinations were not possible in almost 50 per cent of the patients because of the lack of sufficient exfoliation. This information could probably be determined histologically by a single biopsy between the fifteenth and twenty-fifth days.

ULTRAVIOLET MICROSCOPIC STUDIES OF NUCLEIC ACIDS

von Bertalanffy and associates[1] demonstrated the specificity of DNA and RNA staining by acridine-orange with ultraviolet or blue-violet microscopy. In the usual maturation of benign or malignant squamous cells, there is a gradual decrease in cytoplasmic RNA and relatively less diminution in nuclear DNA. Irradiated cells, in contrast, showed more rapid reduction in the nuclear fluorescence, which changed from brilliant yellow to dull olive-green, while the cytoplasm remained bright orange until later in the treatment.

It was noted that even in the pretreatment smears a variable number of malignant squamous cells showed minimal fluorescence. These poorly-fluorescing cells were usually well-differentiated, cornified cells or markedly degenerated cells, which differed from the typical type B cells of Caspersson by the absence of demonstrable nucleoli. There was a gradual increase in these poorly-fluorescing cells during treat-

ment, and, in general, the observations corresponded to the changes in the nucleoprotein patterns of the nuclei noted in smears stained by the Papanicolaou technique.

The examination of nucleoli was facilitated by the acridine-orange technique, since the nucleoli could be distinctly visualized despite the high chromatin content of the malignant nuclei, whereas in the Papanicolaou stained control smears the nucleoli frequently were completely obscured by the nuclear hyperchromasia. The ultraviolet studies demonstrated relatively little change in the size or number of nucleoli during irradiation until the cells reached advanced stages of degeneration or maturation when the fluorescence of the nucleoli faded with that of the other cellular components. It was frequently observed that the nucleolar RNA was the last nucleic acid constituent to fade in fluorescence.

It is worthy of re-emphasis that the "active-appearing" malignant squamous cells, which have diffuse nuclear hyperchromasia and no apparent nucleoli when examined by the standard staining techniques and ordinary light microscopy, do have large and frequently multiple nucleoli, and the apparent increase in nucleolar size reported to occur during irradiation is due chiefly to the unmasking of the nucleoli by the decrease in chromatin density.

EXFOLIATION OF MALIGNANT CELLS

The propensity for desquamation was evaluated by counting the number of malignant cells in relation to the number of benign squamous cells. The smears from over one-half of the patients exhibited abundant cancer cells during the early phase of treatment, with malignant cells comprising 25 per cent or more of the epithelial cells. Twenty-five per cent of the patients consistently had such sparsity of malignant cells that the smears had to be searched diligently to detect any, while the remaining 25 per cent had smears which contained from 5 to 25 per cent malignant cells. Although there were minor variations in the malignant cell populations from day to day in individual patients, the percentage of malignant cells was remarkably constant and showed a definite sequential pattern in most cases. This attribute has been designated by us as one of exfoliation, for, although the smears represented direct scrapings, the fundamental property is still one of cohesiveness. The median values are illustrated in Figure 3.

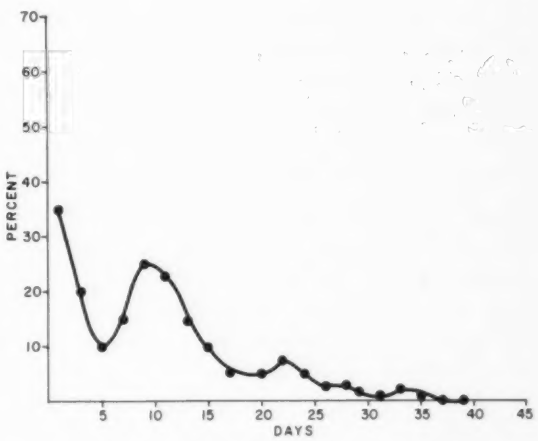

Fig. 3. Median percentage values indicating the number of exfoliating malignant cells during treatment in relation to the number of benign squamous cells in oral smears (40 patients).

During the first few days of therapy there was usually a gradual decrease in the number of cancer cells, characteristically followed by an increase sometime between the seventh and fifteenth days, and not infrequently exceeding the number in the pretreatment smears. This was then followed by a more gradual, but still fluctuating decline. The temporary increase in malignant cells above the pretreatment levels is believed to be the result of decreased cohesiveness rather than stimulation of tumor growth, since the percentages of poorly differentiated cells were not coincidentally increased as would be expected if the latter were true.[12]

There were certain factors which appeared to influence the extent of exfoliation, namely, size, location, gross anatomic type, and the degree of differentiation of

the neoplasms. In general, large, exophytic or poorly differentiated carcinomas exfoliated more than did small, ulcerated or well-differentiated carcinomas. Significant factors would seem to be the size of the tumor surface area, the presence or absence of an inflammatory pseudomembrane (covering ulcerated tumors) which restricts the detachment of malignant cells, and the degree of intercellular adhesiveness which is undoubtedly less in poorly differentiated neoplasms. It must be admitted that some of the cells from very well-differentiated carcinomas may have been mistaken for benign cells. Location also played a role, malignant cells being more abundant in carcinomas of the floor of the mouth than in other locations, even though the tumors of the floor of the mouth were, on the average, smaller and less exophytic than those in other areas.

Although the above factors obviously had some bearing on the extent of exfoliation, even the combination of all of the factors could not adequately explain the differences. For example, tumors which appeared to be identical in location, size, and gross and histologic type often produced completely different smears, one set containing abundant malignant cells, the other practically none. The vigor applied to scraping the surface or the selection of surface to be scraped was not a significant factor, for, if this had been the case, there should have been much greater variation from day to day in individual cases. On the contrary, each patient showed remarkable uniformity in his pattern of exfoliation. The cells may have been more numerous in smears from neoplasms of the floor of the mouth due to trapping of the cells in the dependent portions of the oral cavity, but, then again, exfoliation from some of these neoplasms was minimal.

Our initial observations[12] indicated that neoplasms which exfoliated abundantly were more likely to metastasize than those which did not, as was also noted by Graham[6] in carcinomas of the cervix. Since this feature should indicate lack of cohesiveness, it may also indicate a greater propensity for the cells of such tumors to break off and enter the lymphatics.[12] Our later findings have only partly sustained these observations. Although the median exfoliation of 15 patients who developed metastasis was 15 per cent, while that of 24 patients who have not demonstrated metastases to date was only 5 per cent, the number of profusely exfoliating neoplasms which metastasized (39 per cent) was only slightly greater than the poorly exfoliating neoplasms (29 per cent). These slight differences are probably explained on the basis of better cellular differentiation of more of the poor exfoliators, since it is well known that less well-differentiated carcinomas are more likely to metastasize.

CONVERSION OF SMEARS FROM POSITIVE TO NEGATIVE

A few of the largest neoplasms maintained dense populations of malignant cells throughout treatment, but this was the exception rather than the rule. In most instances the cancer cells became so sparse during the last two to three weeks of treatment that they became difficult to find, there often being only one or two in an entire smear, despite the usual number of benign superficial squamous cells and inflammatory cells. Interpretation also became more difficult, and occasionally it was impossible to differentiate between well-differentiated squamous carcinoma cells and benign squamous cells showing radiation changes, thus necessitating the use of a "suspicious" category.

Over 70 per cent of the patients still had positive or suspicious smears at the end of treatment, almost 50 per cent being unequivocally positive (Table II). These cytologic findings correspond well with the histologic observations of Hall and Friedman,[7] who found persistent tumor in 50 per cent of biopsies from irradiated carcinomas of the mouth or oropharynx.

Graham and Graham[5,6] noted that the presence of malignant cells in vaginal smears at the completion of treatment did not preclude cure, and our findings were

TABLE II

COMPARATIVE VALUE OF ORAL SMEARS AT COMPLETION OF TREATMENT AND ONE TO TWO MONTHS AFTER IRRADIATION

Clinical Status	End of Treatment (55 patients)			Immediate Postirradiation Period (47 patients)		
	Positive	Suspicious	Negative	Positive	Suspicious	Negative
No neoplasm	8	7	6	0	2	17
Primary	14	5	9	13	2	7
Residual neoplasm	9	4	7	9	2	3
Recurrence	5	1	2	4	0	4
Metastases	10	4	4	5	4	6
Dead	9	1	4	6	3	1
Total patients	24	15	16	13	6	28

similar. Eighteen patients who had positive or suspicious smears at this time converted during the immediate postirradiation period (one to three months). Most of these conversions occurred during the first postirradiation month, the tardiest conversion being between the second and third month. The lack of correlation between the presence or absence of malignant cells at the end of treatment and the clinical results is illustrated in Table II. It is readily apparent that smears taken at this time are of relatively little prognostic value, especially if positive.

The significance of the results of examination of smears taken within the first three months following completion of treatment is indicated in Table II, and is in striking contrast to that of the examinations made at the end of therapy. Each of the 13 patients who had positive smears during the postirradiation phase either had residual neoplasm or developed recurrent neoplasm, and 6 have died; only 3 (11 per cent) of the 28 patients whose smears were negative during this phase had residual tumor; only 4 of these 28 subsequently developed recurrent neoplasm, and all but 1 are alive at the time of this report.

DETECTION OF RECURRENT NEOPLASM

Eight patients had what was clinically regarded as recurrent neoplasm. However, 4 of these had positive smears throughout the postirradiation period and their neoplasms are therefore believed to represent residual rather than recurrent carcinoma. The other 4 had negative smears immediately after irradiation; 1 remained negative, 1 reconverted to positive and 2 changed from negative to suspicious when the recurrence developed. The fact that there was only 1 false-negative is heartening, since it was feared that many of the recurrent neoplasms might be entirely submucosal and would, therefore, escape cytologic detection.

INFLAMMATORY CHANGES

Practically all of the smears which contained malignant cells also contained innumerable leukocytes and bacteria, including many within benign and malignant squamous cells, and there was usually a proportionate decrease in the inflammatory cells as the number of malignant cells diminished. The leukocytes were predominantly neutrophilic granulocytes in the pretreatment smears and in those taken during the early phases of treatment, while eosinophilic leukocytes, lymphocytes, and plasma cells appeared in increasing numbers during treatment. The persistence of inflammatory cells after the disappearance of malignant cells usually indicated persistence of ulcers and, when found in postirradiation smears, which were devoid of malignant cells, suggested ulcerative radio-

necrosis. Most of the post-treatment smears from patients without clinical evidence of residual neoplasm were characterized by their tidy, clean appearance, since they consisted exclusively of superficial squamous cells which showed none of the marked degenerative changes seen during and before treatment and were not accompanied by leukocytes, bacteria, and debris. In several instances, recurrent neoplasm was first suspected when a patient whose previous smears had this uninfected appearance suddenly developed smears containing many leukocytes, even in the absence of malignant cells, the latter being found in subsequent smears.

The presence of erythrocytes was less constant and seemed to be related to the vigor used in scraping the lesions. In no instance was bleeding severe enough to interfere with the interpretation of the smears, to require treatment, or to impair healing.

CONCLUSIONS

1. The radiation changes in benign and malignant squamous cells from oral or oropharyngeal carcinomas have been described; these include observations of the nucleic acids by acridine-orange fluorescence microscopy.

2. The radiation response of benign squamous cells was not found to be of practical value in prognosticating the clinical results.

3. *Destruction* of malignant cells by irradiation appears to be more important than radiation-induced tumor *differentiation*.

4. Determination of maturation and cornification indices were of no practical clinical value.

5. Percentage analysis of Caspersson type A and type B cells during treatment correlated well with clinical results.

6. There were marked differences in the exfoliation of malignant cells from neoplasms which were otherwise similar in location, size, gross characteristics, and histologic differentiation. The reasons for these differences remain to be elucidated. Initially reported increased propensity for abundantly exfoliating tumors to metastasize was only partially substantiated.

7. The presence of malignant cells in oral smears taken at the end of treatment does not preclude irradiation arrest, and many patients showed conversion of positive to negative smears following completion of treatment.

8. Oral smears taken during the first three months after treatment are of practical prognostic value. Every patient whose smears were positive during that period was ultimately proved to have residual or recurrent neoplasm, while only 11 per cent of patients with negative smears at that time had residual neoplasm.

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250 KV. ROTATION THERAPY FOR CARCINOMA OF THE ESOPHAGUS USING THE JOHNS HOPKINS SCREEN INTENSIFIER*

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RADIATION therapy by rotation for malignant disease is not a new concept. However, due to the work of Dr. Jens Nielsen[6] of Copenhagen, this form of treatment has become quite popular in recent years, particularly in Scandinavian countries.[3,4] The principle of Nielsen's method of therapy is that the patient is rotated in an extremely narrow beam of radiation, sometimes as small as 1 cm. wide, with the lesion centered at the axis of rotation. The lesion is identified and is watched throughout the treatment time on a fluoroscopic screen, the position of the patient being altered during treatment if the lesion should go out of the field. In this fashion, the skin is spared by using the whole circumference of the body; the integral dose is kept low; the normal tissues are spared as much as possible; and the volume of tissue being treated receives the maximum dose. Even using radiations in the 250 kv. range, a cancerocidal dose can be delivered with this technique. Other methods of rotating the patient or the machine have been developed, but with no other technique can such a narrow field be used or such good control of the treatment area be obtained.

The modification of Nielsen's method which has been adopted at The Johns Hopkins Hospital is in the use of the fluoroscopic screen intensifier with a televised image for control of the treatment zone. This excludes exposure of personnel watching the direct screen through the control window, and obviates the elaborate mirror systems which have been devised with the same end in view. Dark adaptation by the observer is also no longer necessary.

Figure 1 shows a patient seated on a rotating chair with the roentgen-ray machine and screen intensifier in position. Figure 2 shows the viewing panel situated in the control room on which the operator can watch the image throughout treatment without himself being exposed to the radiation. This arrangement was described by Morgan *et al.*[5] as a logical area of usefulness for the screen intensifier and, although not essential to the use of rotation therapy, it has proved to be of tremendous value in determining the accuracy of direction of the beam of radiation and in ensuring centralization of the beam on the desired area.

When the lesion under treatment is a carcinoma of the esophagus, the patient sits on the rotating chair with the axis of rotation at 75 cm. from the focal spot of the 250 kv. roentgen-ray machine and the screen intensifier is placed at the far side of the

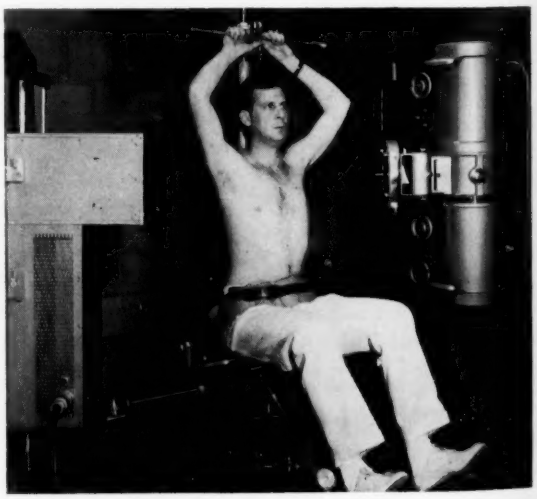

FIG. 1. Patient positioned for rotation therapy.

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Fig. 2. Viewing panel of screen intensifier.

patient. The patient is given a mouthful of barium to be retained in the mouth; the chair is set in motion and, when roentgen rays are generated, the image of the chest appears on the television screen. Instructions are then given to the patient to swallow the barium. The opaque material is visualized on the screen and should remain in the center of the beam throughout the rotation. If it does not do so, the position of the chair is altered accordingly. The chair rotates at a speed of two revolutions per minute and, initially, a total of ten revolutions, or five minutes of treatment time, is given in order to familiarize the patient with the procedure. When the dosage calculations are completed, an estimated tumor dose of 200 r is given daily. These calculations are made during the therapy and will be further discussed below. The size of the treatment field is usually 5 cm. in width at the rotational axis and is of a length corresponding to three times the roentgenologic estimate of the involved area of the esophagus. Because of the angulation of the esophagus in its lower third, lesions of this area naturally will require a wider beam of radiation. The factors used are 250 kv., 0.5 mm. Cu+1.0 mm. Al filter, tumor target distance 75 cm. The half value layer of the beam in current use with these factors is approximately 2.0 mm. Cu. The tube is specially made by the Machlett Company with a very small focal spot of 0.5 cm. diameter, which gives excellent resolution of the image on the television screen.

SELECTION OF PATIENTS

Not all cases of carcinoma of the esophagus have been deemed suitable for treatment by rotation therapy. The full course, lasting some six weeks, entails a not inconsiderable constitutional strain on the patient and we have felt that the general condition of the patient should be moderately good to allow for completion of the treatment. In one instance, conventional anterior and posterior opposing portals were used to reduce the esophageal obstruction and three months later, when the patient's physical condition had improved, a course of rotation therapy was instituted.

The second criterion for treatment by this method which we adopted is the absence of obvious metastatic disease. It was felt that, if the patient has a life expectancy of only a few weeks, there is no justification for a type of therapy which, at best, can only control the primary disease. In such cases, palliative therapy was given with a suitable number of fixed fields and symptomatic metastases were irradiated in a similar fashion.

Thirdly, in lesions of the upper and lower thirds of the esophagus, surgical opinion was sought and all the cases treated by rotational therapy were deemed inoperable by the surgical staff. Several lesions of the middle third of the esophagus, which probably were resectable, were referred for roentgen therapy in order to compare the results of such treatment with those obtained by the formidable operative proce-

dures necessitated by the site of the lesion. The extent of the involvement of the esophagus *per se* was not considered to be a contraindication to radical roentgen therapy in the absence of demonstrable metastases in a patient in fair general health.

TREATMENT TIME AND DOSAGE

Allowing for the initiation of the patient to the procedure and for the time taken in calculating the dosage to the esophagus, a dose rate of approximately 1,000 r per week given in five treatment days was adopted, and a calculated tumor dose of between 5,500 and 6,000 r in five to six weeks was given in most cases.

Many methods of calculating the tumor dose have been described. Most simply, one can take an average measurement of the body diameter at the level of the treated lesion and estimate the dosage from isodose curves and depth dose tables after suitable allowance is made for absorption in the lung tissue. This is unsatisfactory because of the irregularity of the body surface and the difficulty in arriving at an estimate of average transmission through the intrathoracic structures and thoracic wall. Measurements in a phantom constructed to conform to the shape of the body have the same objection.

Wachsmann and Barth[10] devised a calculation system based on the ratio of the transmitted dose rate at a point twice the rotational axis-target distance to the air dose rate at the rotational axis. From a nomogram prepared for the specific physical factors used, the localized percentage tumor dose at the rotational axis can be determined. If the tumor is located at the axis, this then becomes the tumor dose. Theoretically, this seems sound and this method of dosage calculation was employed in the early cases in our series. An attempt was made to obtain a check of this calculation by the use of dosimetric film swallowed by the patient during the rotation treatment and it was found that an approximate correlation was obtained. Subsequently, we obtained a Bomke direct reading dosimeter with an ionization chamber contained at the tip of a narrow bore flexible rubber tube. In theory, this could be placed at the center of the lesion during the rotation and a direct reading obtained of the dose delivered at that point. Unfortunately, in the majority of our patients, the degree of esophageal obstruction was such that they were unable to swallow this tube in the initial stage of their course of therapy. However, we were able to obtain direct readings in 6 patients and, in these, a high degree of correlation was obtained between Bomke measurements and calculation of dosage by the Wachsmann-Barth method. A Siemens dosimeter swallowed by the patient has also given similar readings in 4 patients.

We have, therefore, used the transmission dose method of calculation in the belief that it is an accurate, simple and satisfactory method of dosimetry. It is intended that when further experience is obtained a more detailed report of our dosimetric calculations will be published.

MATERIAL

During the past six years, a total of 57 patients with midline thoracic tumors has been treated by rotational therapy with the image intensifier (Table 1). Of these, 45 patients with carcinoma of the esophagus represent by far the largest group. Three of these were unable to complete the course of therapy; 2 had lesions of the cardia with intrathoracic spread and a third had a bypass operation in which the diseased esophagus was left in place. In this latter patient it was found that irradiation of the esopha-

TABLE I

CARCINOMA CASES TREATED

Site	No.
Esophagus	45
Lung	7
Pharynx	4
Trachea	1
Total	57

Table II

CARCINOMA OF ESOPHAGUS
AGE AND SEX DISTRIBUTION

Age	No. of Cases	Sex		No. of Cases
38	2	Male		39
40–49	7	White	22	
50–59	18	Negro	17	
60–69	13	Female		6
70–79	3	White	3	
84	2	Negro	3	
Average age, 59.4 years				

gus was limited by the presence of a loop of small intestine which had been brought into the chest. One further patient has only recently completed his course of treatment. Thus 41 patients who have had a full course of therapy at least six months ago are available for evaluation.

The age and sex of these patients are shown in Table II. It will be seen that the majority were males and that the highest incidence was during the sixth and seventh decades of life. The histology of the lesions and the site in the esophagus are shown in Table III. Three patients were treated without obtaining a positive biopsy but the clinical and roentgenologic picture was such that there was little doubt of the diagnosis. The greatest number of patients had lesions

Table III

CARCINOMA OF ESOPHAGUS
SITE AND HISTOLOGY

Site in the Esophagus	No. of Cases
Upper Third	5
Middle Third	33
Lower Third	5
Whole Esophagus	2
Histology	
Squamous	35
Adenocarcinoma	2
Undifferentiated	5
Unknown	3

Table IV

CARCINOMA OF ESOPHAGUS
DOSAGE

Dose (r)	No. of Cases
Less than 5,000	7
5,000 to 5,490	6
5,500 to 5,990	12
6,000 and more	20

of the middle third of the esophagus, but a few with lesions of the upper and lower thirds of the esophagus were also treated, and 2 patients had involvement of almost the entire esophagus.

Table IV groups the patients according to the calculated dosage received in the esophagus. Those receiving less than 5,000 r include the 3 who did not complete their course of therapy. The lowest dose given for attempted radical treatment was 3,600 r administered in thirty-four days to an elderly patient who had extensive involvement of the lower and middle thirds of the esophagus. The highest dose recorded was 6,175 r delivered in thirty-five days.

RESULTS OF TREATMENT

SURVIVAL

The survival time of the 41 patients under consideration is shown in Table V. Of the patients who survived more than two years, 1 died thirty-two months after his initial therapy, having developed enlarged mediastinal lymph nodes which were temporarily relieved by the administration of

Table V

CARCINOMA OF ESOPHAGUS
RESULTS

Survival Time (mo.)	Dead	Alive
Less than 6	17	—
6–12	13	3
12–24	3	2
More than 24	2	1
Average survival, all patients		8.7 months
Average survival, patients dead		8.4 months
Average survival, patients alive		10.0 months

external irradiation. He at no time had difficulty in swallowing after treatment but he was troubled by eructation of gas for the last two years of his life. No autopsy was performed on this patient. A second man survived twenty-nine months from the beginning of treatment. He had developed a stricture of the esophagus following treatment which allowed only soft foods to pass. He fed himself largely through a gastrostomy and, after two years without evidence of recurrent disease, it was decided to attempt to dilate the stricture in the upper third of the esophagus. Unfortunately, subsequent to this procedure, he perforated his esophagus at the site of the stricture, developed mediastinitis and died. At autopsy there was no evidence of tumor at the site of the stricture nor of any metastatic disease. A third patient has survived for more than twenty-four months and is still doing very well without any evidence of recurrence.

The average over-all survival of our patients is 8.7 months but at least 3 of the survivors appear to be very well and it is probable that they will survive for several months more. Of those who are dead, the average survival is only 8.4 months and of those still living the average is now ten months. The survival rates are extremely poor but they are at least comparable with those obtained by other modalities in the treatment of carcinoma of the middle third of the esophagus.[1,2,7,8,9] It is submitted that this type of therapy of this lesion will provide a life expectancy comparable with that obtained by a radical surgical procedure[2,8,9] and without the very high mortality associated with operations in this area. Supervoltage therapy has not extended life expectancy significantly beyond that obtained in this series.[1]

The mode of death in those patients who have succumbed is of some interest (Table VI). There was evidence of widespread metastatic disease in no fewer than 15 of these patients. In none was there tumor recurrence at the site of the primary lesion and the majority of these patients were able to swallow relatively normally for the months of life remaining to them. There was definite evidence of local recurrence which led to death in 4 patients and of local recurrence with perforation and subsequent death in 4 others. One patient developed a fistula following esophagoscopy but did not have evidence of disease. Six patients developed strictures at the site of the lesion which contributed to their deaths in that it was not possible to keep the esophagus patent. Four patients subsequently developed lesions elsewhere in the esophagus; 3 of these were at the cardia and 1 in the mid-esophagus, the latter being in a patient who had previously received therapy for a lesion of the upper third of the esophagus.

TABLE VI

CARCINOMA OF ESOPHAGUS
MODE OF DEATH

	No. of Cases
Metastatic Disease	15
Local Recurrence	4
Fistula	5
Stricture	6
Recurrence Elsewhere	4
Unknown	1

One particularly interesting case was a sixty-five year old Negro male who was admitted to the hospital in July, 1955, with almost complete obstruction of the middle third of the esophagus. His general condition was poor and it was decided that he could not tolerate a full course of rotational therapy. He was given a tumor dose of 2,500 r through anterior and posterior fields with dramatic improvement in his symptoms. He was able to swallow without great difficulty and in September his condition had improved to the extent that he was judged to be suitable for radical treatment. A tumor dose of 4,750 r was given in thirty days by rotational therapy, the previously treated areas being shielded with lead during the rotation. His swallowing became almost normal and, at esophagoscopy subsequent to the treatment, no abnormality

was noted. In November, 1956, one year later, he was readmitted to the hospital with symptoms of obstruction and was found to have a polypoid lesion at the cardiac end of the esophagus. On November 5, 1956, this was resected and the stomach was anastomosed to the upper end of the resection which by measurement was proved to have been within the area irradiated one year previously. At the line of section there was no evidence of malignant disease and only minimal changes of radiation fibrosis could be seen. The anastomosis healed well and the patient began to swallow again quite normally. On January 25, 1957, he was found dead in bed at his home. Unfortunately, an autopsy was not obtained but he had been seen by a friend on the previous evening and was then apparently quite well. It is felt that he probably had a cardiovascular accident but a breakdown of the suture line cannot of course be excluded.

COMPLICATIONS

In Table VII are shown the complications which occurred in this series of patients. Six of our cases developed strictures at the site of the primary lesion following the course of treatment, these strictures being sufficiently severe to impede the swallowing of solid foods. One stricture was resected and the tissue showed evidence of dense fibrosis but no active tumor (Fig. 3 and 4). In 1 case, an attempt to dilate the stricture two years following the completion of therapy led to a perforation and subsequent death. In the other 4 patients, gentle dilatation of the stricture kept the esophageal lumen temporarily patent but subsequent dilatation became increasingly necessary and the patients gradually succumbed from inanition and cachexia. One woman was enabled to swallow for a period of fifteen months following treatment with dilatation at approximately weekly intervals. In retrospect, a resection of the fibrotic area might have been beneficial but, in 4 of the patients, the primary lesion was at the level of the arch of the aorta and it was felt that resection would have been impossible. Alternatively, a bypass operation might be considered.

TABLE VII

CARCINOMA OF ESOPHAGUS
COMPLICATIONS

	No. of Cases
Stricture	6
Fistula	5
Pneumonitis	1

Five patients in our series developed fistulae at the site of the primary lesion subsequent to treatment. In those cases in which autopsies were performed, there was evidence of persistent tumor at the site and in 3 of these the fistulous openings were into major blood vessels closely adjacent to the esophagus. This complication is of

FIG. 3. Specimen of carcinoma of esophagus five months after administration of 5,500 r.

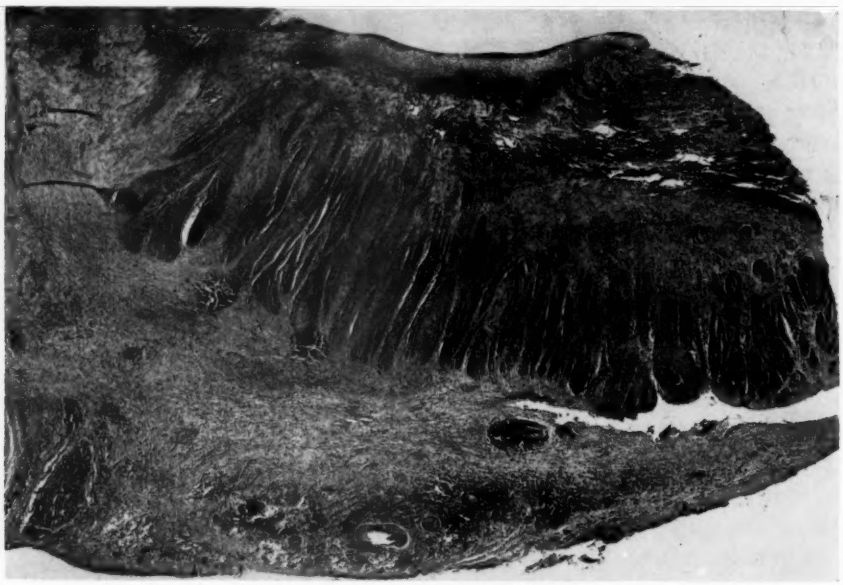

FIG. 4. Same specimen as in Figure 3 showing gross fibrosis but no active tumor.

course a common one in lesions of the middle third of the esophagus which are not treated.

Perhaps unexpectedly, the finding of severe radiation pneumonitis was confined to 1 case. A transient shadow was seen in the pulmonary parenchyma in 1 patient but he was entirely asymptomatic. The patient who did develop pneumonitis was greatly distressed by dyspnea but his symptoms rapidly cleared under steroid therapy. He subsequently developed a spontaneous pneumothorax which was treated by drainage with complete re-expansion of the lung. The etiology of this complication is not clear. In none of the 41 patients, nor in fact in any of the patients treated by this technique, was the constitutional upset associated with radiation therapy a problem sufficient to warrant interference with the normal course of therapy. The occasional slight nausea in a few patients was readily controlled by the administration of one of the antiemetic preparations.

POST-THERAPY ESOPHAGOSCOPY

Many patients have in the past been treated by radiation therapy but there are few observations in the literature on the local results of treatment or the effect on the esophagus. When a stricture was excised in 1 patient early in this series, it was clear that the esophagus, exclusive of the stricture, was quite healthy and we felt that little harm could ensue in other patients from esophagoscopy following treatment. Accordingly, four weeks after completion of treatment, several of these patients were subjected to esophagoscopy and biopsies were taken from the area where the tumor had originally been identified. These results will be published separately. A total of 14 patients were esophagoscoped subsequent to treatment and the biopsies were entirely negative, showing only scarring, in all but 1 of these. The patient who showed a positive biopsy after treatment died of his disease three months later. In all of the cases a characteristic circumferential contraction of the esophageal lumen, with smooth walls, was seen. A bougie was passed through this constriction which was found to be readily distensible. Biopsies were then taken from the area below the constriction. No complications ensued from this procedure and, while a negative biopsy is of little significance, a positive finding soon after treatment is obviously a useful

prognostic indicator and it is felt that this procedure is of considerable value.

DISCUSSION

During the past six years, some experience has been gained in the treatment of lesions in the midline of the body, chiefly carcinoma of the esophagus. Using a screen intensifier technique with televised image, it has been possible to follow the lesion throughout the course of treatment on the screen and thus to reduce the width of the treatment field and to ensure that the lesion is within the treated area at all times. Greatest experience has been gained with lesions of the middle third of the esophagus, it being felt that the very high mortality associated with the surgical resection of lesions in this area did not justify operative treatment. The survival of the patients treated with the technique described in this paper cannot be considered satisfactory but the palliative value of the treatment is certainly substantial, since the great majority of the patients were able to swallow normally for the remainder of the time that was left to them.

It is felt that this relatively simple procedure affords better palliation than surgery and, although no long term survivals have yet been obtained with this technique, late recurrence at the site of the lesion has not occurred. Those who have died after long periods of freedom from disease have done so either from metastases which would not have been prevented by surgery or, in 1 instance, by an over-enthusiastic attempt at dilatation of an incomplete stricture. No patient died as a result of the procedure and the complications arising from the treatment are those common in untreated carcinoma of the esophagus or are relatively insignificant in relation to the seriousness of the primary disease. Radiation pneumonitis was not a serious complication except in 1 patient and in his case the period of morbidity was only about two weeks.

This technique has, in this hospital, been used in association with a 250 kv. machine and it is difficult to believe that with supervoltage any better results will be obtained. However, the screen intensifier technique can be readily employed with a 2 mev. machine with a small focal spot. This no doubt is a rational extension of the technique but in this series the tumor dose to be delivered to the primary lesion has never been limited by the skin reaction or by the development of pneumonitis.

SUMMARY

1. The use of the Johns Hopkins screen intensifier in the treatment of carcinoma of the esophagus by rotational therapy with a 250 kv. machine is described.

2. With this technique a very narrow beam of radiation can be used and treatment of the desired area throughout the course of therapy can be ensured.

3. The results of this treatment over a period of six years are not gratifying in terms of survival but the palliative effect of the treatment is at least as good as that associated with surgical resection or with other methods of radiation therapy. Furthermore, there is no mortality associated with this procedure and, when a larger series of patients is treated, it is confidently expected that an occasional long term survivor will appear.

4. The possible value of post-treatment esophagoscopy is discussed. In a series of patients so investigated no complications ensued.

5. The problem of dosimetry in rotational therapy is also discussed briefly and it is concluded that the transmission dose calculations give a value closely approximating the true tumor dose as measured by an ionization chamber placed at the site of the lesion.

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ENDOBRONCHIAL MALIGNANT LYMPHOMA*

REPORT OF FIVE CASES IN ADULTS

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THE pulmonary manifestations of malignant lymphoma have been fully described in the literature with respect to mediastinal disease, pleural involvement and parenchymal infiltration. The small number of reports concerning endobronchial invasion with atelectasis has attracted the present authors' attention. The majority of these deal with isolated cases and, insofar as we have been able to determine, only 2 cases have been previously reported in the radiologic literature.[7,8] Soulas[8] described an interesting case of obstructive emphysema secondary to partial occlusion of the right mainstem bronchus by Hodgkin's granulomatous tissue. He performed 4 bronchoscopic studies over a ten month period and only the fourth biopsy was diagnostic of Hodgkin's granuloma, showing Reed-Sternberg cells. A case of complete occlusion of the left mainstem bronchus by Hodgkin's granuloma was reported by Paviot *et al.*[6] The occlusive mass appeared at postmortem examination as coagulated mucus but microscopic examination disclosed a true granuloma. In a case presented by Heatly,[3] atelectasis of the right lower lobe was found to be caused by a smooth, slightly reddish mass resembling a bronchial adenoma. Although the biopsy of this mass was suggestive of lymphoma, a thoracotomy was required to establish a positive diagnosis of Hodgkin's disease. Hardin's[2] case illustrated a progressive atelectasis of the entire right lung with intermittent relief following irradiation of the mediastinum. The radiation dose was not specified and the disease subsequently became refractory to this form of therapy.

The article by Moolten[5] presents an accurate description of the pathologic nature of pulmonary Hodgkin's disease. Detailed postmortem study was reported in 8 cases and in 4 granulomatous infiltration of the bronchi was demonstrated. In a fifth case, a polypoid mass projected into and completely occluded the right mainstem bronchus. This was thought to result from an unusual accident of growth which altered the course of the disease and produced early death.

We have encountered 5 cases presenting this complication and do not regard it as an unusual growth variant. Rather, it should be considered a true facet of systemic lymphomatosis, the developement of which may be facilitated by initially inadequate irradiation of the mediastinum.

The pertinent data referable to the pulmonary aspect of these cases are presented in the following case histories and the radiation therapy data are given in Table 1.

REPORT OF CASES

Case 1. R. G., a thirty year old Negro female, was admitted to the M. D. Anderson Hospital on January 3, 1957, with chief complaints of progressive dyspnea and severe, irritating nonproductive cough of one month's duration.

A diagnosis of generalized Hodgkin's disease was established on June 3, 1954, on the basis of cervical and mediastinal lymphadenopathy and a positive right cervical lymph node biopsy. On July 15, 1954, radiation therapy was started and 1,200 r was delivered to the mediastinum through parallel opposing fields and an additional 1,500 r to the right neck. Treatment was completed to both areas over a sixteen day period. On February 8, 1955, the mediastinum was re-treated for recurrence. A dose of 2,000 r

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Table I

ROENTGEN THERAPY DATA

Patient		Tumor Dose	Survival Post Irradiation	Cause of Death
Case I* R.G.	(a) 250 kv., H.V.L. 3.1 mm. Cu	1,900 r	9 mo.	Acute congestive heart failure; no postmortem examination
	(b) Betatron	1,100 in 5 wk.		
Case II L.L.	250 kv., H.V.L. 3.1 mm. Cu	2,030 r in 36 da.	8 mo. follow-up, negative chest roentgenogram but aggressive disease present in other areas	Lost to follow-up
Case III† V.E.	(a) Rotational 220 kv., H.V.L. 2.75 mm. Cu	2,000 r in 24 da.	18 mo.	Peritonitis from perforated peptic ulcer, prepyloric; residual endobronchial disease
	(b) 250 kv., H.V.L. 3.1 mm. Cu	2,050 r in 24 da.		
Case IV J.V.B.	250 kv., H.V.L. 3.1 mm. Cu	2,100 r in 38 da.	6 mo. follow-up, negative chest roentgenogram but aggressive disease present in other areas	Lost to follow-up
Case V E.Y.	250 kv. grid H.V.L. 1.1 mm. Cu	2,400 r in 38 da.	15 da.	Uncontrolled congestive failure, myocardial tumor infiltration; thrombosis of superior vena cava

* Previously administered therapy for mediastinal lymphadenopathy: 1,200 r at 250 kv. in 16 days in July, 1954; 2,000 r at 250 kv. in 10 days in February, 1955.

† Previously administered therapy for mediastinal lymphadenopathy: 1,200 r in air to each of 15×15 cm. anterior and posterior ports in 1950.

was delivered through parallel opposing anterior and posterior ports over a ten day period.

Physical examination revealed an acutely ill female extremely dyspneic and coughing at frequent intervals. Moderate discrete, firm, nontender lymph nodes were noted in the left cervical, axillary and supraclavicular areas. Coarse ronchi were heard over the right chest and there was dullness with absent breath sounds over the entire left chest. The liver was 2 fingerbreaths enlarged and the spleen not palpable.

The clinical impression of atelectasis of the left lung was confirmed by a chest roentgenogram (Fig. 1*A*). Bronchoscopy disclosed complete closure of the left mainstem bronchus at the level of the carina by an irregular growth of firm, nodular, grayish-white tumor tissue. The biopsy specimen from this area showed an atypical lymphatic infiltrate compatible with malignant lymphoma.

The patient was placed in an oxygen tent on the day of admission because of severe dyspnea and six days later radiation therapy to the mediastinum was started. After one week of therapy, marked improvement allowed discontinuation of oxygen. A total dose of 3,000 r was given over a period of five weeks. A roentgenogram of the chest at the completion of therapy showed complete aeration of the left lung and the patient was discharged (Fig. 1*B*).

Six months later, the patient was re-admitted in a terminal condition and expired on the third hospital day. A portable chest roentgenogram showed only a left pleural effusion. Permission for postmortem examination was denied.

Case II. L. S., a forty year old Negro male minister, was admitted to the M. D. Anderson Hospital on June 1, 1956, with complaints of severe weakness, dyspnea, a dry irritating cough and edema of both lower extremities of several weeks' duration. A diagnosis of lymphosarcoma was established eleven months previously.

On physical examination, dullness and absent breath sounds were noted over the entire left lung. There was a suggestion of several deep

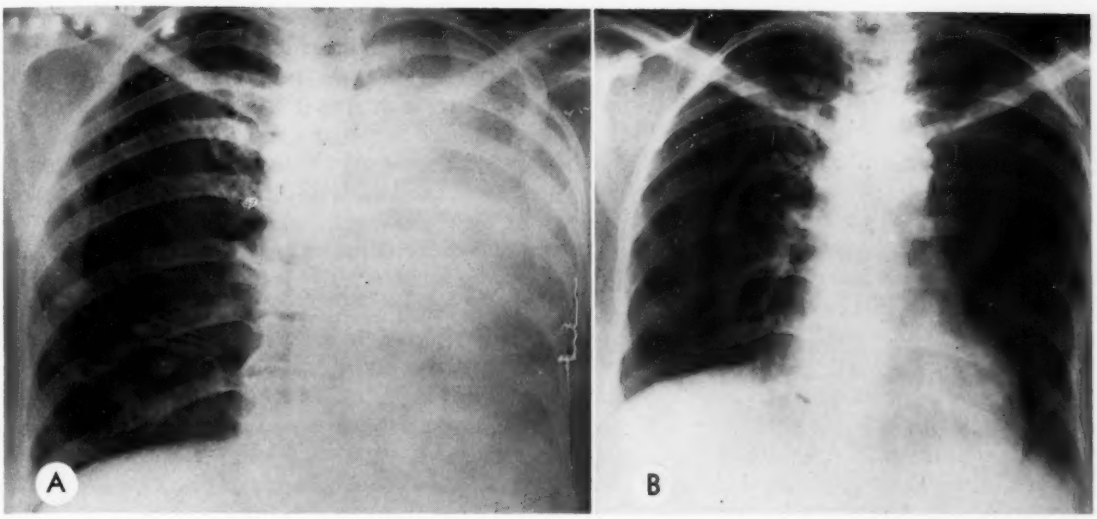

Fig. 1. Case I. Endobronchial Hodgkin's disease. (*A*) Atelectasis of the left lung. (*B*) Complete re-expansion of the lung following roentgen therapy. (The findings were identical in Case II.)

masses in the midabdomen though the liver and spleen were not enlarged. A roentgenogram of the chest demonstrated massive opacification of the left lung field with a shift of the heart and mediastinum to the left. Bronchoscopy showed complete occlusion of the left mainstem bronchus about 1 cm. below the carina by a firm mass of grayish-white tumor tissue. This was biopsied and histologic examination revealed a white cellular infiltrate of lymphomatous character. Although Reed-Sternberg cells were not seen, the general pattern of the tumor suggested Hodgkin's disease.

Radiation therapy was given through anterior and posterior mediastinal fields for a minimal dose of 2,030 r in thirty-six days. After two weeks of therapy, dyspnea was considerably improved. After three weeks of therapy, a roentgenogram of the chest showed complete re-expansion of the left lung.

Two months following discharge, the patient was admitted again to the hospital with complaints of extreme weakness and subcutaneous nodules over the chest, abdomen and groin. Physical examination disclosed the presence of hard subcutaneous nodules scattered over the chest and abdomen, measuring from 1 cm. to 5 cm. in diameter. A biopsy of one of the abdominal nodules showed an atypical lymphatic infiltration compatible with lymphosarcoma. A repeat chest roentgenogram showed both lungs to be expanded with no evidence of mediastinal lymphadenopathy. Therapy consisted of 40 mg. of nitrogen mustard intravenously in one dose. The patient was discharged twelve days later at his own request with no improvement noted. Six months later progression of the skin nodules was noted, but a chest roentgenogram was negative. This patient, unfortunately, has been lost to follow-up and is presumed dead.

Case III. V. E., a forty-five year old housewife, was admitted to the M. D. Anderson hospital on November 24, 1954, with complaints of progressively worsening dyspnea and dry cough of five months' duration.

A diagnosis of Hodgkin's disease was established during October, 1957, at another hospital by cervical lymph node biopsy. Radiation therapy was given at the same institution to the mediastinum and we were informed that the dose was 1,200 r in air to anterior and posterior fields over a period of twenty-one days.

Physical examination revealed an ill-appearing middle-aged white female having considerable difficulty breathing. Ronchi and wheezing were noted over both lung fields. Small shotty lymph nodes were found in the cervical, axillary and inguinal areas. The liver and spleen were not enlarged. A chest roentgenogram showed a large mediastinal mass, predominantly left sided, and a definitely enlarged right hilar shadow. The transverse measurement of the mass was 18 cm.

On November 25, the day following admission, 30 mg. of nitrogen mustard was given intravenously in a single dose and within two days dyspnea was much improved. The patient

was discharged on the seventh hospital day and seen in the out-patient clinic two weeks later. She was virtually free of symptoms except for mild nausea. A repeat chest roentgenogram showed regression in the size of the mediastinal mass from 18 cm. to 12 cm.

During the next four and one-half months, the clinical situation remained unchanged. After this period, a progressive increase in the mediastinal mass was observed with no associated symptoms. It was decided to re-treat the mediastinum with radiation therapy. Using 220 kv. rotational therapy, 2,000 r was delivered to the mediastinum over a twenty-four day period ending June 10, 1955. Serial chest roentgenograms demonstrated no significant regression of the mediastinal mass, and on September 14, the patient was re-admitted and 50 mg. of nitrogen mustard was given in one dose. After seventeen days of hospitalization, she was discharged to the out-patient clinic. Although a significant diminution occurred in the size of the mass, it was less than the first nitrogen mustard induced response. This remission lasted four months after which an irritative cough and exertional dyspnea occurred. However, she was not re-admitted until October 12, when cough and dyspnea were severe at rest and associated with left pleural effusion. A chest roentgenogram after the removal of pleural fluid showed atelectasis of the left lower lobe. Bronchoscopy disclosed a symmetric, constrictive process beginning above the superior dorsal orifice which appeared to be extra-mucosal, firm, dull-gray and bled a little with instrumentation. Biopsy disclosed only atypical fibrosis. Laminagrams through the left hilar area showed complete obstruction of the lower lobe bronchus, the end of the air column appearing smooth and tapered, suggesting extrinsic pressure. After two weeks of supportive therapy, the patient was discharged improved, nitrogen mustard and radiation therapy being withheld. Some two weeks later, re-admission was again necessary for cough and dyspnea and a repeat bronchoscopy was done with the same gross and microscopic findings as previously observed. Thoracentesis of the left chest yielded 2 liters of fluid and considerably relieved the dyspnea. On November 23, radiation therapy was started to the left mediastinum through anterior and posterior fields. Over a period of four weeks, 2,050 r was delivered. For a period of two months following the completion of therapy, the patient did well after which dyspnea again supervened and was not alleviated by a left thoracentesis. Over an interval covering the next eleven months, 6 additional hospitalizations were necessary for chronic productive cough, progressive dyspnea and recurrent left pleural effusion. Thoracentesis was necessary during each admission and, in addition, 30 mg. of nitrogen mustard was instilled into the left pleural cavity on August 6, 1957 and 20 mg. was given intravenously on September 23, 1957. Two bronchoscopies as well as bronchography (Fig. 2) were performed during this period but yielded no additional information.

The final admission was on April 18, 1958, at which time the patient was seen in the out-patient division and was obviously terminal. She expired the following day.

Postmortem examination disclosed a perforated prepyloric ulcer with acute peritonitis. There was generalized lymphadenopathy as well as foci of tumor in the liver and spleen. The entire left lung was completely atelectatic and bilateral pleural effusion was present. The left mainstem bronchus was infiltrated by scattered zones of tumor tissue. The upper lobe orifice was

FIG. 2. Case III. Endobronchial Hodgkin's disease. Bronchogram demonstrating complete obstruction of left lower lobe bronchus with peripheral atelectasis.

very small and the lingular divisions were closed by dense grayish-white desmoplastic tumor tissue. The lower lobe bronchus was patent but showed tumor infiltration in the peribronchial zone. It is to be noted that endobronchial disease was first noted in October, 1956, nine years after the positive establishment of Hodgkin's disease, and was manifested by cough, dyspnea and atelectasis of the lower left lobe.

Case iv. J. V. B., a sixty-five year old white farmer, was referred to the M. D. Anderson Hospital on November 22, 1955, with the chief complaint of hemoptysis of three weeks' duration. A diagnosis of Hodgkin's granuloma was established at another hospital on January 24, 1954. A chest roentgenogram at this time disclosed right hilar and paratracheal masses.

Physical examination revealed an elderly white male. Small firm lymph nodes were palpable in both axillary areas but there was no cervical or inguinal lymphadenopathy and the liver and spleen were not enlarged. Fine moist rales were heard in the right mid-lung field anteriorly and posteriorly.

Chest roentgenograms and laminagrams showed a large thick-walled cavity in the right parahilar area with a zone of solid infiltration inferiorly and medially (Fig. 3*A*). Bronchoscopy disclosed an irregular grayish-white tumor mass beginning just below the spur of the right upper lobe orifice and extending down the bronchus intermedius. The lumen was so narrowed as to not permit passage of the bronchoscope more than a centimeter below the carina. Biopsy disclosed the presence of an atypical round cell infiltrate which was felt to be compatible with malignant lymphoma. On December 13, 1955, radiation therapy was started, pneumoperitoneum having been established the previous day. An estimated dose of 2,100 r was delivered to the cavity area and right bronchus over a thirty-eight day period and hemoptysis was completely controlled (Fig. 3*B*).

Six months later, the patient was re-admitted to the hospital because of weakness and a 35 pound weight loss. Physical examination disclosed no enlarged lymph nodes or hepatosplenomegaly and the chest was clear. A roentgenogram showed only fibrotic scarring in the previously treated area. An osteolytic area was found in the right ilium. Because of intermittent pyrexia with temperature spikes to 102° F., nitrogen mustard, 20 mg. intravenously, was administered and the patient was discharged two weeks later improved. He has been lost to follow-up examinations and is presumed dead.

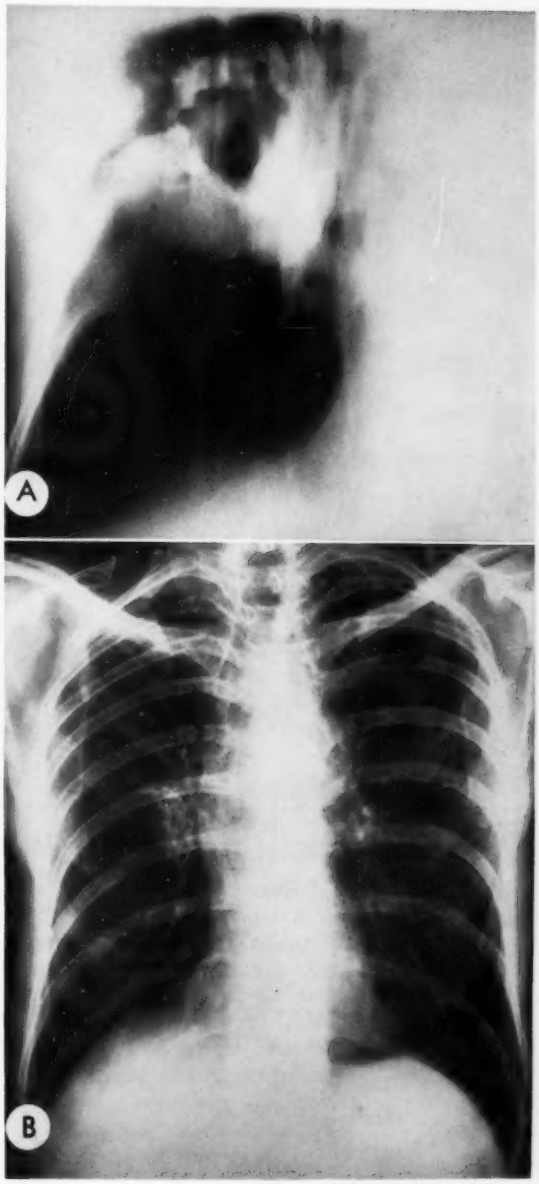

Fig. 3. Case iv. Endobronchial and parenchymal Hodgkin's disease. (*A*) Laminagram showing inflammatory necrosis of parenchymal mass following bronchial obstruction. (*B*) Complete healing with minor residual fibrosis is demonstrated after a course of roentgen therapy.

Case v. E. Y., twenty-six year old Negro male janitor, was admitted to the M. D. Anderson Hospital on February 19, 1958, with chief complaints of dyspnea, irritating cough

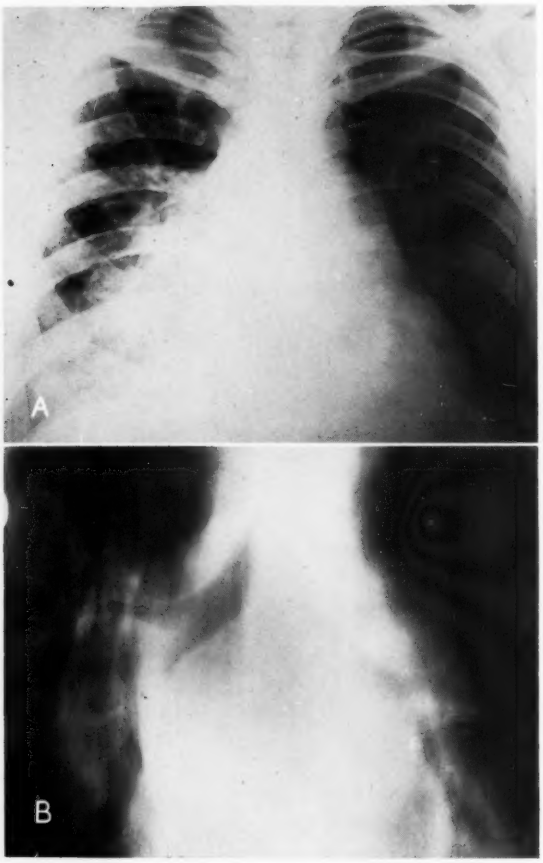

FIG. 4. Case v. Mediastinal, endobronchial and parenchymal lymphosarcoma. (*A*) Conventional chest roentgenogram showing cardiac enlargement and right mediastinal and parenchymal masses. (*B*) Mediastinal laminagram showing conical narrowing of mainstem bronchus below origin of upper lobe division and segmental atelectasis of lower lobe. Extrinsic pressure is evident on left mainstem bronchus.

and wheezing respirations of one week's duration. A diagnosis of lymphosarcoma was established six months previously at another hospital.

A chest roentgenogram showed a right hilar and mediastinal mass with infiltration into the right lung field which was felt to be due to lymphosarcoma. Also, a small right pleural effusion was observed. Thirty milligrams of nitrogen mustard were given intravenously on the second hospital day and the patient was discharged on February 26, 1958, markedly improved with dypsnea virtually absent and cough well controlled. On March 6, 1958, the patient was re-admitted complaining of dyspnea and a dry persistent cough of several days' duration. Breath sounds were distant over the right lung field and expiratory wheezes and ronchi were scattered throughout both lung fields.

A conventional chest roentgenogram (Fig. 4*A*) showed a large mediastinal mass and an intrapulmonary mass on the right side. Laminagrams of the right chest showed a sharp conical narrowing of the right mainstem bronchus immediately below the upper lobe division with segmental atelectasis of the lower lobe (Fig. 4*B*). Gross cardiac enlargement was also present. On the fifth hospital day, bronchoscopy was accomplished under local anesthesia and the bronchus intermedius was noted to be about 75 per cent occluded by a grayish-white nodular tumor mass. Biopsy showed the presence of a round cell infiltrate which was thought to be compatible with the original diagnosis of lymphosarcoma. Sputum cytology examinations were highly suspicious for bronchogenic carcinoma.

On March 24, radiation therapy was instituted to the mediastinum using a grid technique in the 250 kv. range. One week later, marked improvement was noted in breathing and oxygen was discontinued. Therapy was continued until April 24, at which time a tumor dose of 2,400 r was delivered to the mediastinum. At this time, further therapy was withheld because of recurrent dyspnea with increasing edema of the neck, face and upper extremities. Angiocardiography was performed and this revealed complete occlusion of the superior vena cava. This was regarded as secondary to thrombosis rather than tumor and so anticoagulant therapy was instituted; however, the patient continued to worsen and expired on May 9, 1958.

Postmortem examination showed thrombotic occlusion of the superior vena cava with tumor invading its wall, extensive mediastinal lymphoma with invasion of the heart and complete patency of the right and left mainstem bronchi. Histologic examination of the right mainstem bronchus showed a patchy infiltrate of lymphosarcoma tumor tissue with prominent foci of necrosis. The character of the tumor tissue of the mediastinal lymph nodes as well as of the wall of the superior vena cava was that of lymphosarcoma, lymphocytic type, while that of the heart was reticulum cell sarcoma.

DISCUSSION

The clinical picture of endobronchial malignant lymphoma is suggested by a dry, irritating cough, frequently quite severe and associated with dyspnea, in a patient with an established diagnosis of lymphoma. This was noted in 4 of the 5 cases presented. Hemoptysis was the initial complaint in the remaining case (Case IV). The roentgen demonstration of atelectasis in such patients usually indicates the diagnosis, although other potential causes of collapse must be excluded by detailed clinical histories. The atelectasis may involve the entire lung or may be lobar or segmental in distribution. Contrary to the usual opinion, detectable mediastinal lymphadenopathy need not be present nor is the pulmonary collapse often related to mechanical pressure by enlarged or matted lymph nodes. In general, endobronchial lymphoma seems to be a separate manifestation of pulmonary Hodgkin's disease, although in some instances direct spread from adjacent involved lymph nodes may play a part in the production of the atelectasis. However, it should be borne in mind that the range of roentgen findings may be quite diversified as evidenced by the demonstration in separate cases in this series of a parahilar cavity and a mediastinal mass with pulmonary infiltration.

The preferred treatment of endobronchial lymphoma is roentgen therapy and it may be used in palliative or definitive fashion, depending on the general condition of the patient, aggressiveness of the disease and the degree of spread. In general, the philosophy of treatment is to deliver an initial dose of sufficient magnitude so that it will not be necessary to re-treat the same area at a later date. Since the amount of irradiation necessary to open a bronchus and partially clear it of tumor is not very great, the expectant survival of the patient becomes the foremost consideration in deciding dosage. The tumor dosage necessary to sterilize an area of lymphomatous nodes is open to some debate. In general, it may be stated that the tendency is toward higher values in recent years. At the M. D. Anderson Hospital and Tumor Institute, it is felt that a tumor dose of 3,000 r in three to five weeks with an additional 1,000 to 1,500 r to residual masses, when necessary, is required to achieve sterilization. Doses of this magnitude, when delivered initially, seldom result in recurrence in the treated area. Cases I and III had received radiation therapy for mediastinal lymphadenopathy prior to developing endobronchial disease and the doses administered fell short of this arbitrary minimum. Hence, these cases are considered treatment failures in that it is felt that recurrence of the mediastinal disease with the endobronchial complication might have been prevented. In Cases II, IV and V, the presenting pulmonary picture was dominated clinically by the endobronchial deposits and the disease in each of these instances was virulent and aggressive. In these particular situations, the initial radiation therapy should not be considered definitive since the prognosis for life beyond nine months to one year is poor. A tumor dose of 2,000 to 2,400 r in thirty-six to thirty-eight days has been found quite adequate to open the bronchus and control pulmonary symptoms. It must be emphasized that these patients are quite ill, daily tolerance to roentgen therapy is variable and general supportive measures (oxygen, fluids, blood, frequent suctioning) are necessary if the patient is to survive the treatment.

Case III deserves special mention because of the long survival (ten and one-half years) coupled with the unusual response to therapy. Over a three and one-half year period, 4 courses of nitrogen mustard and 2 courses of mediastinal irradiation were undertaken and the response to chemotherapy proved slightly superior than to roentgen therapy. The first remissions induced by nitrogen mustard lasted a total of nine months and objective diminution of mediastinal lymphadenopathy was noted each time. The remaining 2 courses of

nitrogen mustard gave only a transitory benefit lasting a few weeks. The courses of mediastinal irradiation controlled symptoms for a total of four months, but produced no objective changes in the chest roentgenogram. This is the opposite of the expected therapeutic result in that irradiation is usually the superior modality for the control of focal manifestations of lymphoma.

These 5 cases, constituting examples of bulky intraluminal growth or bronchostenosis, are but one type of endobronchial involvement in malignant lymphoma. The more common form is a granulomatous panbronchitis or peribronchitis which may be associated with a granulomatous interstitial pneumonia.[5] Attention is not called to the involvement of the respiratory passages in this form since the bronchi become part of the disease process "without ever having the lead."[1] In the remaining type, scattered plaques and nodules are the primary manifestations and are usually multiple and diffuse. Heretofore, this has been a postmortem finding except when the nodules become sufficiently large to produce obstructive symptoms.

SUMMARY AND CONCLUSIONS

1. Four cases of malignant lymphoma presenting as mass endobronchial lesions and one presenting as bronchostenosis are described.

2. The complication is characterized by persistent, dry, irritating cough, usually associated with dyspnea and the physical and roentgen findings of atelectasis. The roentgen picture does not differ in any way from that of atelectasis due to other causes; however, it has not been widely emphasized that endobronchial disease is usually responsible for the atelectasis and that pressure from enlarged mediastinal lymph nodes does not play a singificant part in the bronchial occlusion.

3. Bronchoscopy revealed obstructive nodular lesions in 4 cases and an extramucosal constriction in the remaining case. Bronchoscopic biopsy was definitive in 1 case only.

4. Criteria for adequate roentgen therapy are postulated and it is urged that such treatment be given initially to uncomplicated mediastinal lymphadenopathy. Failure to do so may result in recurrence of the disease in the treated area with complicating endobronchial involvement. This was believed to have occurred in 2 of the presented cases.

5. Endobronchial involvement dominated the initial pulmonary manifestations in 3 instances. This is probably indicative of virulent disease and the prognosis of survival beyond nine months to one year is poor. Therapy in palliative doses is usually adequate to control obstructive pulmonary manifestations in such cases.

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ADDENDUM

Since the submission of this report 2 additional patients with endobronchial invasion have come to our attention.

The first of these, a sixty-one year old white female, complained of a spastic, irritating, nonproductive cough with increasing dyspnea of three months' duration. Lymphosarcoma had been previously diagnosed from a left cervical lymph node biopsy on July 1, 1952. Physical examination disclosed very distant breath sounds in the left lung field and the chest roentgenogram showed bilateral emphysema which was increased as compared to previous examinations dating back several years. Bronchoscopy disclosed a lymphomatous occlusion of the left mainstem bronchus at the level of the carina. Bronchoscopic secretion was classified as malignant cells, Grade v, and the biopsy as reticulum cell sarcoma. Nitrogen mustard, 20 mg. intravenously, has presently controlled respiratory symptoms and radiation therapy is to be administered.

The second patient, brought to our attention through the courtesy of Dr. Leonard C. Doubleday, was a fifty year old white female with the

chief complaint of pain in the chest. A conventional roentgenogram of the chest disclosed a small quantity of fluid on the left in association with atelectasis of the left lower lobe. In the lateral projection, a small anterior mediastinal mass was demonstrable. Bronchoscopic studies showed a tumor of the left lower lobe bronchus which was interpreted by the pathologist as undifferentiated squamous cell carcinoma. Irradiation was administered and, after a tumor dose of 1,000 r, complete re-expansion of the left lung was obtained and therapy was discontinued. The patient was relatively well for approximately one year at which time mediastinal adenopathy recurred as well as skeletal disease. The patient went downhill rapidly and expired from systemic lymphosarcoma. Review of the original slides indicated that lymphomatous tissue had been responsible for obstruction of the left mainstem bronchus.

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ROENTGEN THERAPY IN WEGENER'S GRANULOMATOSIS*

A CASE REPORT

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WEGENER'S granulomatosis is a rare disease of undetermined etiology characterized by (a) granulomatous ulcerative lesions in the upper respiratory tract, (b) widespread granulomata, seen frequently in the lung, kidney, and spleen, and (c) widespread vasculitis and glomerulitis. The onset is insidious, beginning with nasal obstruction, crusting, epistaxis, or antral pain, or lower respiratory tract symptoms such as cough, pleurisy, or hemoptysis. The disease occurs most often in young or middle aged adults and runs a course averaging five months until death. The longest survival has been reported as four years.[13] Death is usually caused by renal involvement.

Some aspects of the condition closely resemble malignant granuloma of the nose,[1,4,5,11,12,14] whereas others appear more like periarteritis nodosa.[12,13] No bacterial or viral agent has been implicated. Most authors infer that an immunologic reaction must be considered as the cause of the disease,[2,7,8] but the evidence is not conclusive.

In treating these patients, antibiotics and steroids have been used. Radiation therapy has produced a temporary response in malignant granuloma of the nose,[4,6,9,11,12] but has been used in only a limited number of cases of Wegener's granulomatosis. In these instances, however, irradiation produced at least temporary regression of the lesion.[4,5] Walton,[13] in a recent concise review of the subject, held the belief that the treatment of choice in Wegener's granulomatosis is radiation therapy to the local lesion, together with suitable antibiotics to control secondary infection. He stated that steroids should be withheld until the local lesion has healed so that defense against infection of the open lesions is not hindered. Some authors,[2,7,10] on the other hand, make no mention of radiation therapy.

In the patient reported here, roentgen therapy produced good temporary regression of local lesions, but the ultimate outcome was, as usual, death.

REPORT OF A CASE

The patient was a forty-four year old white housewife who was first seen in the Radiation Therapy Department of the University of California Medical Center in April, 1958, with a two months' history of painless swelling in the right parotid gland region. Occasional warmth of the skin overlying the mass had been noted, but there had been no real pain or tenderness. Sialography had been reported as negative. The swelling did not appear to be the usual parotitis. A biopsy was not done.

After the mass had enlarged slightly during a period of two months, and had been diagnosed as chronic parotitis, roentgen therapy to a dose of 1,100 r in air (1,300 r on skin) was delivered in fifteen days using 250 kv. peak, Thoraeus III filter, half value layer of 3.2 mm. Cu and target skin distance of 50 cm. The size of the mass decreased during treatment and it was no longer detectable two months later.

When seen in August, 1958, the patient had been hoarse for three weeks and had some edema in the left side of the larynx, asymmetry of the neck, and generalized swelling of the right temporalis muscle. During that time she had developed a fever, enlarged bilateral submandibular lymph nodes, and purulent exudate in the pharynx. She was admitted to the hospital and an enlarged submental lymph node was removed for biopsy, since the possibility of a lymphoma was being considered. The pathologist reported "marked hyperplasia of lymph node showing focal necrosis and eosinophilic infiltration." Ulcerations appeared on the hard palate and large masses in the tonsillar regions were covered with exudate. Histologic examination of hypertrophied oropharyngeal lymphoid

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bands showed a granulomatous process of "unclassified" type, with ulceration. The blood cell count, chest roentgenogram, urinalysis, and bone marrow tests were normal. With nonspecific supportive care, her general condition improved and the patient was discharged after three weeks in the hospital.

She was readmitted on October 6 with a productive cough, fever, elevated white blood cell count, and roentgenographic evidence of patchy pneumonitis at the right lung base. There was edema of the larynx, lymphoid hyperplasia in the posterior pharynx, and white plaques over the posterior pharynx and larynx. A tracheotomy was performed because of respiratory embarrassment. Biopsy of a posterior cervical lymph node revealed "reticulo-endothelial hyperplasia" and a subsequent biopsy of the hypopharynx was reported "chronic nonspecific granulomatous ulcerative inflammation." Treatment consisted primarily of penicillin and prednisone. The laryngeal edema decreased, pneumonitis subsided, and the tracheotomy tube was removed. She was discharged on prednisone after a hospital stay of seven weeks.

On January 4, 1959, the patient was readmitted because of fever and inability to swallow. At that time, she had granulomatous lesions of the lateral pharnyx with general mucosal hypertrophy and superficial ulceration of the aryepiglottic folds. Since the original therapy to the parotid area had led to marked regression, roentgen therapy was given to both sides of the neck, using the same factors as in the previous treatment of the parotid area, delivering 400 r in air (500 r skin dose) to each side in ten days. The symptoms were relieved temporarily and the pharyngeal and laryngeal edema was greatly reduced. Ten days later, however, there was increased edema in the submental and submandibular areas, with recurrent difficulty in breathing and swallowing. Roentgen therapy of 600 r skin dose in six days was given to the submental area, which resulted in amelioration of symptoms and in regression of the swelling. At this time, nodular densities in the lower lung fields were noted in roentgenograms and reported as "consistent with Wegener's granulomatosis."[3] Although the densities increased, the patient's fever and symptoms subsided and she was discharged on February 2, 1959.

On March 14, 1959, the patient was readmitted because of high fever, weakness, dyspnea, and swelling of the neck tissues. Her pharynx was again injected, with slight hypertrophy of lymphoid tissues. A sinus tract had developed from the left pyriform sinus into the soft tissues of the neck and was demonstrated, by contrast roentgenography to extend to the level of T1 (Fig. 1). Roentgenograms of the chest showed multiple nodular densities in the lungs, one with cavitation (Fig. 2). A new biopsy of the pharyngoesophageal area showed "non-specific chronically inflamed granulation tissue." Edema of the tissues surrounding the trachea caused marked narrowing of the airway down to the level of the coryna. Treatment was continued with prednisone and antibiotics. During the last three days of life, the patient received roentgen therapy to the neck and superior mediastinum, 100 r skin dose daily, but she died of respiratory obstruction on April 3, 1959.

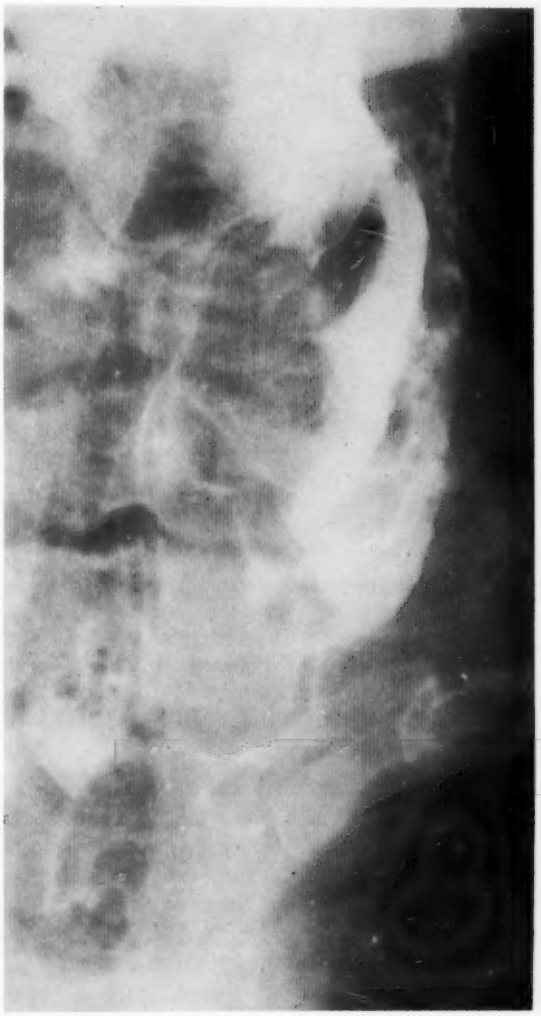

Fig. 1. Contrast medium outlines a fistulous tract from the left pyriform sinus to the level of T1.

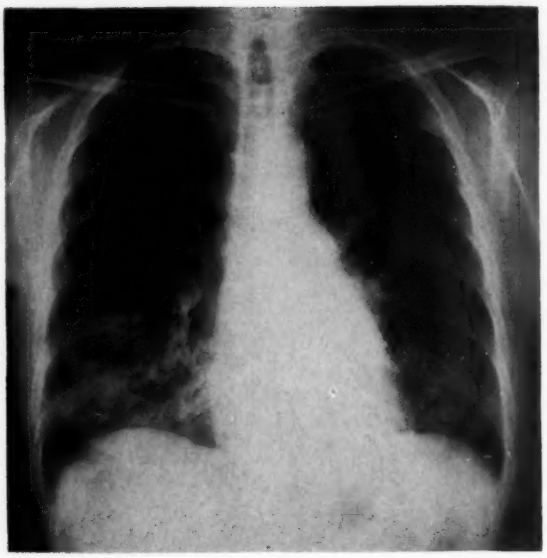

FIG. 2. Chest roentgenogram, at the time of final hospital admission, shows mutliple nodular densities in both lungs with cavitation near the right hilus. In addition, there is some consolidation in the right middle lobe. Note the narrow airway in the larynx.

Postmortem examination showed granulomatous lesions in the nasopharynx, hypopharynx, larynx, and trachea. The epicardium showed profuse infiltration with round cells, eosinophils, and the suggestion of a pseudogranulomatous pattern in focal areas. In the mediastinum, a granulomatous reaction involved the great vessels and the roots of the lungs, with a gross residual alveolar pattern in the background, and eosinophilic, necrotic, hyalinized material. Peribronchial infiltration with round cells gradually changing to eosinophilic infiltration, central necrosis, and epithelioid cells, and panperivascular infiltration of arteries and veins were seen. The parotid glands appeared normal except for postmortem autolysis and periductal fibrosis. The kidneys showed occasional focal round cell infiltration in the perivascular areas, and glomerular tufts showed adhesions to Bowman's capsule, some engorgement and edema, and round cell infiltration. The final diagnosis was Wegener's granulomatosis.

SUMMARY

Wegener's granulomatosis, a fatal disease of questionable etiology, produces granulomatous, ulcerative lesions in the upper respiratory tract, widespread granulomata, and widespread vasculitis with glomerulitis. Treatment with antibiotics, steroids, and roentgen therapy produces temporary palliation only.

A patient is reported in whom roentgen therapy produced dramatic, although only temporary, relief from upper respiratory lesions, supporting Walton's statement that radiation therapy is of value in treating the local lesions of this disease.

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THE EARLY DIAGNOSIS OF PROSTATIC MALIGNANCY BY THE USE OF P^{32}*

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CARCINOMA of the prostate is the most frequent of the malignant neoplasms found in men over fifty years of age, and the third in incidence as a cause of death. The early diagnosis of this malignant tumor, while the process is still confined to the gland and curable, is extremely difficult at the present time. The most common screening procedure used is the digital examination, which is unreliable in early carcinomas. In one reported series, only 23 per cent of early malignant tumors were correctly diagnosed by palpation.[3] Jewett[4] compared the digital rectal examination findings in 108 benign and 103 malignant nodules of the prostate and was unable to find any discernible difference.

Tissue examination is, of course, the ideal method of diagnosis. However, tissue obtained by transurethral resection is unreliable for diagnostic purposes because this procedure does not always remove tissue from the posterior lobe—the most frequent area of involvement. Perineal needle biopsy is a more satisfactory method but is a blind procedure. The area of involvement, especially if small, may be readily missed. Biopsy through the rectum is an operating room procedure requiring anesthesia. While the results are satisfactory, the morbidity is somewhat high. Open perineal biopsy is the best method. It is, however, a major operative procedure.

The necessity for additional diagnostic methods to supplement the digital examination, yet not requiring surgery, becomes apparent.

We have, therefore, tried to develop a quick, simple, and reliable screening test which will aid in determining when more definitive diagnostic measures are needed. The test is based on the differential absorption of radioactive phosphorus (P^{32}) by benign and malignant tissue. These differences in absorption are measured by a small Geiger-Müller probe which is inserted into the rectum over the area of the prostate.

BIOLOGIC BACKGROUND

P^{32} is a pile-produced isotope with a half life of 14.3 days. It is a pure beta emitter with the beta particles having a maximum energy of 1.7 mev.

Marshak,[7] in 1940, found high concentrations of P^{32} in tumor nuclei of mice lymphoma transplants. He concluded that the greater uptake in the tumor cells was due to their increased mitotic activity and was not a specific characteristic of this tumor.[7]

Others have shown that the higher pickup of P^{32} was due to its intracellular incorporation into desoxyribonucleic acid, ribonucleic acid and other nucleotides which are present in higher concentrations in malignant cells. This was demonstrated in such tumors as those of the ovary, breast, stomach, and prostate.[6,9,10,11] Along with the increased formation of nucleic acids, their metabolic activity has been shown to be higher by increased P^{32} turnover. Schulman *et al.*[11] demonstrated that the increased rate of P^{32} turnover was limited to the cancer cells themselves, and that these changes were not demonstrable in the surrounding tissue.

In 1941, Kenney *et al.*[5] introduced the concept of the "differential absorption ratio" (D.A.R.). This is the ratio of P^{32} absorbed by the tissue in question in relation to the amount the tissue would have

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contained if the isotope had been equally distributed throughout the body. He was able to show significant differential absorption ratios in breast adenocarcinoma, osteogenic sarcoma, and lymphosarcoma.

Inflammatory tissue has also been shown to absorb P^{32} in different amounts than malignant tissue. Thomas *et al.*[14] induced inflammatory lesions in the eyes of rabbits and found that after an initial increase in absorption, due to the increased vascularity associated with inflammation, the uptake gradually approached that of the normal eye over a period of minutes. For this reason it was felt that there would be no difficulty in differentiating inflammatory from malignant lesions. Low-Beer[6] was able to demonstrate differences between breast carcinomas and mastitis.

Histologic differences in cells do not affect the counting rate. The concentration of the isotope within the cell is reflected by the count rate, which is dependent upon physiologic changes and biochemical activities of the cell, not upon morphologic characteristics.[9]

CLINICAL BACKGROUND

Selverstone *et al.*[12] used P^{32} for localization of brain tumors, inserting a specially designed Geiger-Müller probe into the brain substance.

Low-Beer[6] was the first to apply external scanning to the breast. Because of the limited range of P^{32} beta rays in tissue, this method is limited to lesions greater than 3 to 4 mm. in diameter and no deeper than 5 to 6 mm. from the surface. In his first report of 197 patients he used the criterion of a pickup greater than 25 per cent over that of normal tissue as indicative of malignancy. In this series he had but one false positive and three false negative results.[6]

Others have applied similar techniques to eye lesions. Many feel that this test will probably find a useful place in ophthalmology.[15] There are, however, limitations to the study in this area, *e.g.*, movements of the patient's eyes, errors in technique and the short range of the P^{32} beta rays.[1] Because of this, a negative test here does not exclude malignancy; however, a positive one is strongly suggestive of it.[1]

METHOD

Twenty-nine consecutive patients admitted to the genitourinary ward who were to have various procedures necessitating biopsies or sections of the prostate gland were selected. All were over forty years of age. A dose schedule of 5 μc of P^{32} per kilogram of body weight was used. It was given intravenously to preclude variations in absorption. The dosage employed here is comparable to that in previously reported studies on eye and breast lesions. A Selverstone-type brain probe attached to a count rate meter was used.

The prostate gland was divided for recording purposes into four quadrants. The patient was examined as in any routine rectal examination. The probe was then introduced along the finger and each quadrant of the gland was scanned separately. The readings which were recorded were those taken in that part of each quadrant with the highest count rate. Additional readings were taken over any suspicious nodule. The count was recorded only when the rate meter gave a constant reading of double the time constant selected. In our series, 20 seconds was used.

DISCUSSION

This experiment was set up to determine whether malignant areas of the prostate would pick up significantly greater amounts of P^{32} than normal tissue, and whether this difference could be detected by external counting.

Normal tissue must be present in the prostate gland for this test to be valid, since there can be no absolute values to indicate malignancy. The normal prostatic tissue of the individual thus serves as his own control.

The results of the study are given in Table 1. The microscopic report confirmed the scanning interpretation in every case.

Count rates of greater than 50 per cent

TABLE I

RESULTS OF SCANNING FOR P^{32} UPTAKE

Patient	Right Upper Quadrant	Right Lower Quadrant	Left Upper Quadrant	Left Lower Quadrant	Impression from P^{32} Study	Clinical Impression	Pathologic Diagnosis
1	500	600	500	600	B	B	B
2	900	800	800	700	B	B	B
3	300	240	460	(600)	M	M	M
4	320	380	(480)	(500)	M	M	M
5	240	300	320	(480)	M	M	M
6	680	740	820	680	B	B	B
7	(600)	300	240	200	M	M	M
8	400	500	510	520	B	B	B
9	220	240	280	300	B	M	B
10	220	200	260	250	B	B	B
11	450	400	420	400	B	M	B
12	140	140	130	150	B	B	B
13	160	170	140	160	B	B	B
14	(540)	380	300	280	M	M	M
15	440	420	380	400	B	B	B
16	200	220	180	160	B	B	B
17	400	380	370	300	B	B	B
18	200	200	180	240	B ?	B	M ?
19	240	(380)	300	280	M	M	M
20	230	160	(360)	230	M	M	M
21	320	240	(420)	300	M	M	M
22	380	380	400	380	B	B	B
23	200	200	180	150	B	B	B
24	280	280	280	260	B	B	B
25	220	280	280	250	B	B	B
26	180	200	220	200	B	B	B
27	340	260	260	300	B	B	B
28	320	320	240	300	B	B	B
29	360	320	320	380	B	B	B

Note: All numbers under various quadrants are in counts per minute.
Parentheses about a number indicate a significant count rate.
B = Benign.
M = Malignant.

SUMMATION OF RESULTS

	Impression from P^{32} Study	Clinical Impression	Pathologic Diagnosis
Malignant	8	10	9
Benign	21	19	20
Total	29	29	29

over supposedly normal tissue were considered indicative of malignancy. The data were then broken down into two groups on this basis—one designated "malignant" and the other "benign."

A chi-square test was performed which showed that the differences in our diagnosis from those found at microscopy may be attributed to chance variations in our readings. No significant difference between the two could be found (Table II).

An *analysis* of the *variance* was under-

TABLE II

CHI-SQUARE X^2

	P^{32} Test Results (P_o)	Pathology (P)
Benign	21	20
Malignant	8	9

$$X^2 = \sum \frac{(P_o - P)^2}{P} = \frac{(21-20)^2}{20} + \frac{(8-9)^2}{9} = .16$$

Note: .16 is not significant.

taken to isolate the factor of individual patient differences in counting rates. The intrinsic variability of the benign and malignant groups was then compared (Table III).

With the factor of patient variation eliminated we would expect that if there were no other factors present except experimental error (variations of equipment, differences in reading of the counts, etc.) there would be no significant difference between the two groups. However, the intrinsic variability of the malignant group was six times that of the benign group. This fact precludes the difference between the two groups as being due to chance. There must, therefore, be another factor present causing this variability, namely, the presence of cancer in part of the gland.

If there is no normal tissue present, a differential absorption cannot be obtained and malignancy cannot be diagnosed by this means. This supposition was tested in several patients with known diffuse involvement of the prostate. As was expected, counts were uniform throughout the gland and no diagnosis could be made by our technique.

Nodules are ideal for evaluation by this method. Two patients in our series had nodules which were clinically believed to be malignant. P^{32} uptake studies failed to show any differential pickup and our impression was confirmed by biopsy, which showed these nodules to be benign.

The time at which the procedure was performed was not found to be critical. The patients were initially examined over varying time intervals ranging from 10 minutes after injection to over a week. The highest readings were obtained in the 10 to 20 minute intervals, probably due to the high concentration of the isotope in the vascular

TABLE III

ANALYSIS OF VARIANCE

	Sum of Squares	*df*
Total Variability	$\sum X^2 - \frac{(\sum X)^2}{N}$	$N - 1$
Variability between Men	$\frac{(\sum X_m)^2}{n_r} - \frac{(\sum X)^2}{N}$	$n_m - 1$

X = each individual value.
N = total number of observations.
n_r = number of readings for each man.
n_m = number of men.

$$\text{Experimental Error } \Sigma X^2 - \frac{(\Sigma Xm)^2}{n_r N - n_m}$$

MEN CONSIDERED AS HAVING CANCER

	Sum of Square	*df*	Mean Square Variance
Total Variability	4,754	31	
Variability between Men	2,766	7	395
Experimental Error	1,988	24	82.8

The intrinsic variability of the cancerous men is $T_c^2 = 82.8$
$T_c = 9.1$

MEN CONSIDERED AS HAVING BENIGN PROSTATE

	Sum of Square	*df*	Mean Square
Total Variability	26,264	83	
Variability between Men	25,374	20	1,269
Experimental Error	890	63	14.13

$T_B^2 = 14.13$ or $T_B = 3.7$

Utilizing the "F" test to determine whether the difference between the two variants is due to chance,

$$F = \frac{T_C^2}{T_B^2} = \frac{82.8}{14.1} = 5.9$$

This result is highly significant even at the 1 per cent level.
Note: all basic values have been divided by 10.

bed of the prostate and the immediate surrounding areas.

In our study we found that the most reproducible and most reliable results were obtained in the 24 to 48 hour period, since variability of blood supply to the gland was eliminated. Count rates could also be successively duplicated with greater accuracy during this period. This was also the interval in which the greatest differentiation between benign and malignant areas was obtained. The examination can be performed at one's convenience any time during the 24 to 48 hour period since counts do not appreciably vary during this span of time.

There are two major limiting factors to this study. First, the test is inherently limited by the range of the P^{32} beta rays in tissue. If the lesion is not within 5 to 6 mm. of the examining finger it will not be detected by the probe. The second main difficulty can be attributed to the design of the probe used in this series. The Selverstone-type probe which was used can lead to three different sources of error: (1) Because of its low sensitivity there will be low count rates which can lead to statistical inaccuracies. (2) The tip is bulbous and is sensitive throughout its entire surface. This factor, before it was discovered, led to erroneously high readings in the upper quadrants of the prostate gland in patients with large hypertrophied glands. In these cases, the finger was removed from the probe tip in an attempt to get the probe in the upper part of the gland. With removal of the finger, the probe received impulses not only from the prostate gland but from the surrounding rectal mucosa. This can lead to false positives and must be guarded against. (3) Since the tip is bulbous, differences in finger pressure result in varying amounts of the surface indenting the gland, thus changing the counting area. This theoretically can lead to changes in count rate.

It is felt that the technical difficulties can be overcome with a properly designed probe. Such a probe would consist of a pancake-type tip, sensitive in only one plane and having a high sensitivity in the beta range of P^{32}. A flexible stem would also be desirable. With such a probe, the accuracy and reliability of this test should be greatly enhanced.

SUMMARY

A new approach to the diagnosis of early prostatic malignant neoplasms using radioactive phosphorus is described. The technical limitations of the study and the equipment used are described. Technical improvements in the equipment are suggested. Although further experience with this test is needed, we feel that it is potentially an accurate, simple, and reliable diagnostic aid which should prove valuable in detecting early prostatic malignant tumors.

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USE OF A Cs^{137} STANDARD OF SPECIAL DESIGN TO CALIBRATE SCINTILLATION SPECTROMETERS FOR CLINICAL I^{131} MEASUREMENT*

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THE adoption of gamma-ray spectrometry techniques to eliminate scattered and background radiation in clinical I^{131} measurements has become widespread.[1–4] The complexity of the required equipment has introduced the major problem of assessing the reliability of results obtained by personnel who usually have a superficial knowledge of electronics and nuclear physics. The physician can only have complete confidence in the measurements if a simple and reliable method of calibration is adopted. It is especially desirable that this calibration be quantitative enough that a percentage deviation in the calibration reading correlates with the same percentage deviation in the sample when the deviations are instrumental.

In the Radioisotope Service Clinic of the Houston Veterans Administration Hospital, we have worked out a procedure for calibration which satisfies this requirement. The procedure involves simple switching between a specially prepared long-lived Cs^{137} standard and the I^{131} sample. The simplicity of switching is a major feature of the method, since there must be no possibility of interjecting uncorrelated deviations in sample and standard by introducing the judgment of the operator in setting pulse-height-analyzer biases, amplifier gain, etc., between readings. The second major feature of the method is the introduction of scatter broadening into the Cs^{137} gamma ray spectrum by embedding the source in an aluminum scattering cylinder. It is this feature that allows quantitative comparison between deviations of sample and standard. The thirty year Cs^{137} with a single gamma ray has proved a more effective standard than "mock iodine"[2] using Ba^{133}.

The calibration procedure has been in use for over two years. Consistency of measurement within two per cent has been achieved on I^{131} samples in which activities have been accurately determined by established assay procedures.

METHOD

Amplifier Pulse-Voltage Divider. Since Cs^{137} and I^{131} emit respectively 660 kev. and 360 kev. gamma rays, a two position voltage divider is used at the output of the linear amplifier. In one position the total pulse voltage output of the amplifier is delivered to the pulse height analyzer. In the other a factor 360/660 is introduced so that the 660 kev. gamma ray can be analyzed in the same channel as the 360 kev. gamma ray. This is done with a single switch on the operator's panel, one position being used for I^{131} measurements and the other for Cs^{137}. Unquestionably, there are many ways to make a pulse voltage divider. We have used a tap on the cathode resistor of the cathode follower at the amplifier output. This method proved simple and effective.

The circuit is shown in Figure 1. On position 1 of the switch, the analyzer receives the pulse voltage developed by the cathode follower; on position 2 it receives a fraction approximately equal to $r_2/(r_2+r_1)$ of the pulse voltage. Due to stray capacitance and the finite input impedance of the analyzer, the ratio $r_2/(r_2+r_1)$ cannot be made exactly equal to the ratio 360/660. Final resistor values must be found by trial and error after observing the pulse spectra of Cs^{137} and I^{131} at the two switch positions.

In equipment where the amplifier output cathode follower was part of an in-

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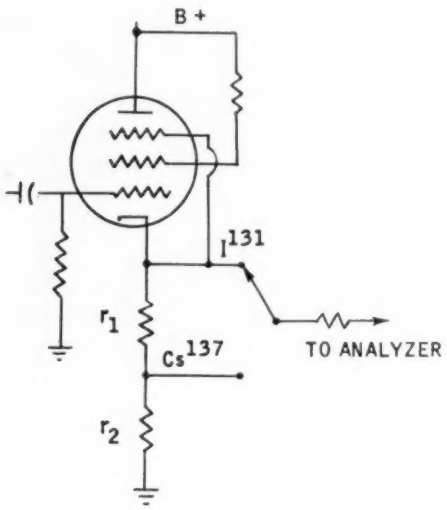

FIG. 1. Diagram of voltage divider system.

verse feedback loop, it was necessary to insert an additional cathode follower as a voltage divider in order not to disturb the feedback. Since this tube drew only a few milliamperes, the addition was not deleterious.

A minor unsolved problem in our equipment lies in the need to modify the ratio $r_2/(r_1+r_2)$ slightly when photomultiplier tubes are replaced. Since replacements have been necessary only after one or two years of use, the recalculations and recalibrations have not proved a major inconvenience.

Pulse Height Analyzer Bias Calibration. A small but important part of the calibration procedure is the monitoring and adjusting of the pulse height analyzer biases. Gain and bias are independent system parameters. In evaluation of system performance, it is necessary to know that the biases are correct before the Cs^{137} standard and overall reading can be taken as a measure of gain stability. A simple and inexpensive pulse generator is used to check the pulse height analyzer bias settings whenever there is doubt about system performance or at intervals dictated by experience. Satisfactory generators are available commercially or can be constructed from circuits described in the literature. In equipment where the pulse amplifier and pulse height analyzer were incorporated in a single electronic unit, it was found useful to incorporate a simple pulse generator in that unit.

The Cs^{137} Standard Source. It is not sufficient to bring the 660 kev. gamma ray of the Cs^{137} standard into the pulse height analyzer channel at the settings used to measure I^{131}. It is also necessary that fluctuations in amplifier gain and channel biases produce the same fractional change in count rate for the Cs^{137} standard as for the I^{131} sample. Details of the pulse spectra of the two radioisotopes must be examined to see if this is possible. Figure 2 shows a comparison of typical pulse spectra obtained from a Cs^{137} point source and an I^{131} sample in the usual form of a 30 ml. water solution. The resolution for the Cs^{137} gamma ray was 9.1 per cent; *i.e.*, the full width of the peak at half height was 9.1 per cent of the position of the maximum measured along the pulse height axis. The data

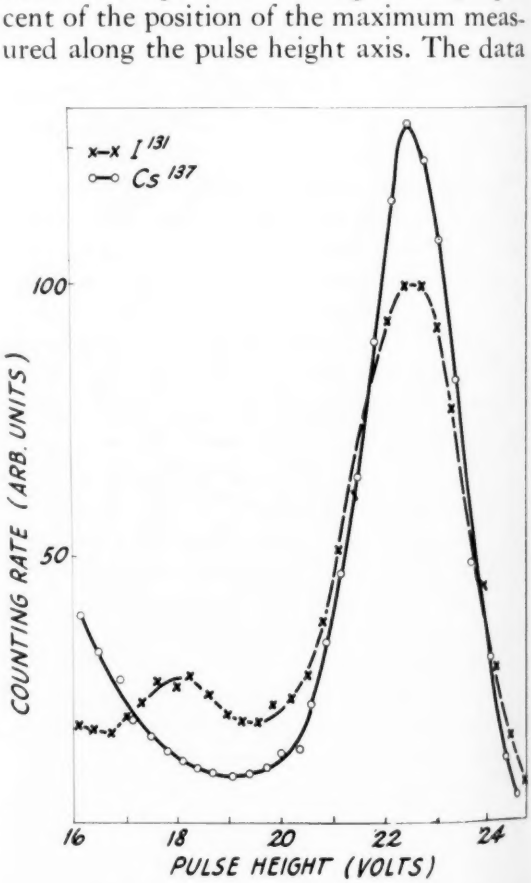

FIG. 2. Pulse spectra of Cs^{137} point source and I^{131} standard source in 30 ml. water.

were taken with half volt channels and a gain such that the peak was at 60 volts, so that the widths of the analyzer channels did not affect the resolution. Abscissas were then reduced to bring the peaks to 22.5 volts, the value used in actual uptake measurement. The peak of Cs^{137} is of course narrower because of photomultiplier statistics.

The ordinates of the spectral curves of Figure 2 are proportional to counts per second per volt pulse height interval. Therefore, the area under a curve between any two points on the pulse height axis is a measure of the contribution to the counting rate from that interval in the spectrum. The curves are normalized to have the same area between 19.0 volts and 26.0 volts pulse height, because in our I^{131} measurements we include the spectrum between 19.0 and 26.0 volts by using a 7 volt channel with the lower bias at 19 volts. The ordinate at 19 volts is approximately equal to gain or loss of counts by a 1 volt downward or upward shift in the lower bias. It is easily seen that the 1 volt shift has a larger effect percentagewise on the I^{131} reading. By actual measurements, the change is 7 per cent for I^{131} as compared to 3 per cent for the Cs^{137} point source. A change in gain which shifts the peaks in the channel likewise has a correspondingly larger effect on the I^{131} reading.

Figure 3 shows a comparison between the same I^{131} spectrum and a Cs^{127} pulse spectrum obtained when the Cs^{137} source is embedded in a 1 inch diameter aluminum rod with $3\frac{1}{2}$ inches of aluminum between source and detector. Again the areas under the curves between 19 and 26 volts are the same. The change in the cesium spectrum from Figure 2 to Figure 3 in the 19 volt region shows the effect of Compton scattering by the aluminum. The cesium spectrum in Figure 3 approximates the I^{131} spectrum at 19 volts fairly well. The spectrum of Figure 3 is that of a standard source actually adopted. If the baseline of a 7 volt channel is actually varied for both I^{131} and this Cs^{137}-in-Al source with all other settings as in actual uptake measurements (*i.e.*, both peaks at 22.5 volts on the appropriate selector switch positions, etc.) the counting rates obtained as a function of baseline in the neighborhood of the 19 volt operating point are shown in Figure 4*b*. Figure 4*a* shows the results of gain variation with baseline remaining constant. A satisfactory parallelism between the curves is seen to exist, so that the Cs^{137}-in-Al source of Figure 3 constitutes a satisfactory standard.

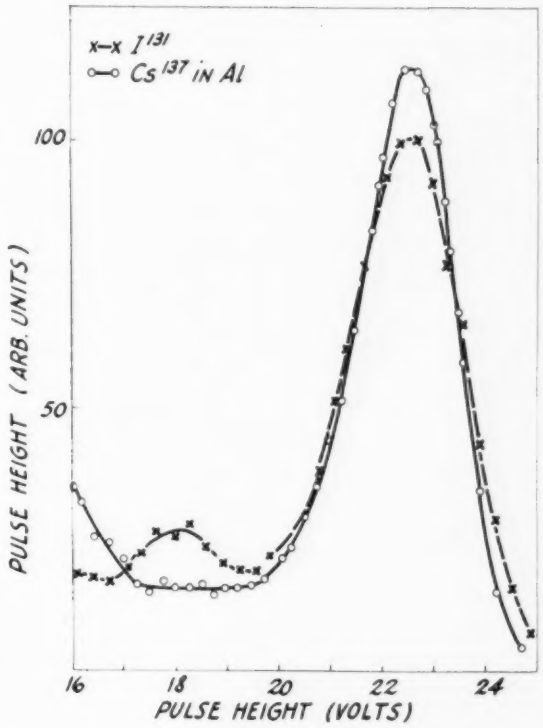

FIG. 3. Pulse spectra of Cs^{137} point source in aluminum scatterer and the I^{131} standard source.

Figure 5*a* shows the physical arrangement of the Cs^{137}-in-Al source in use with our detector; Figure 5*b* is the diagram of the cesium standard and detector. The standard is shown in relation to the scintillation crystal, lead shield and locating device of an I^{131} uptake instrument, as it is used in the standardization of that instrument.

The problem of tailoring the Cs^{137} spectrum to the I^{131} spectrum can only be attacked after a choice of operating condi-

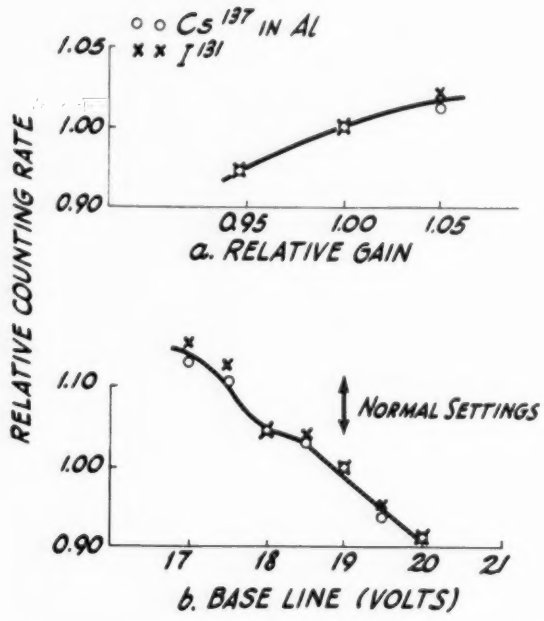

FIG. 4. Relative variations in counting rate. (*a*) Small gain variations with constant normal baseline. (*b*) Small baseline variations with constant normal gain. Standard geometry and 7.0 volt channel width in both cases.

tions is made. The fact that we have chosen the aluminum dimensions to give best correspondence between the spectra at 19.0 volts was governed by the choice of the 19–26 volt interval in the I^{131} spectrum with the peak at 22.5 volts. The choice has some arbitrariness. Considerations of counting rates in relation to I^{131} dosage, stability of counting rates in the face of small gain and bias variations, and in fact the achievable shaping of the Cs^{137} pulse spectrum were all factors in the choice. Some attention will be paid in later sections to this point.

DESIGN OF THE Cs^{137} STANDARD

While many scattering geometries are possible, consideration was limited to cylindrical masses of aluminum with the Cs^{137} source embedded on the cylinder axis. Only cylindrical geometries were considered because success with more complicated shapes appeared to depend too critically on the judgment of the operator in positioning the source under the detector. After preliminary success with several cylinders was achieved, considerable effort was devoted to understanding the relation between the form of the spectrum and the mass and dimensions of scattering material. Calculation appeared more promising than measurement where the pulse distribution was observed with 10 per cent energy resolution at 660 kev. due to photomultiplier statistical broadening. Numerical calculations were made for a number of cylinder sizes. The calculations were checked in the case of several large cylinders where the scatter broadening was measurable with the available resolution. A few of the results are given below to show what may be accomplished.

To estimate the scatter spectrum, single scattering events of the type shown in Figure 6 were considered in the calculations. The source is located at A on the cylinder axis AA'. To reach the detector after being once scattered through angle θ, a photon was assumed to leave the source at angle θ and to be scattered into approximate parallelism with the cylinder axis. The scattered spectrum reaching the detector could be calculated on this approximation in terms of the electron density in the aluminum, the solid angle subtended by the detector, and the differential cross section for Compton scattering per unit solid angle through an angle θ. The differential cross section for Compton scattering and the relation between θ and E, where E is the energy of the scattered photon, can be found in standard texts on nuclear physics.* Scattered photons reaching the detector with energy in a small interval centered at E were assumed to yield a Gaussian pulse height distribution with 9.1 per cent full width at half maximum centered at the pulse height equivalent of E.

The radiation emerging from the end of the cylinder consists of a mixture of scattered and unscattered radiation. The pulse spectrum in the detector will depend on the ratio of scattered to unscattered radiation. The effect of the unscattered radiation in

* For example: SEGRE, E. Experimental Nuclear Physics. Part II. Volume I. John Wiley & Sons, Inc., New York, 1953, p. 319.

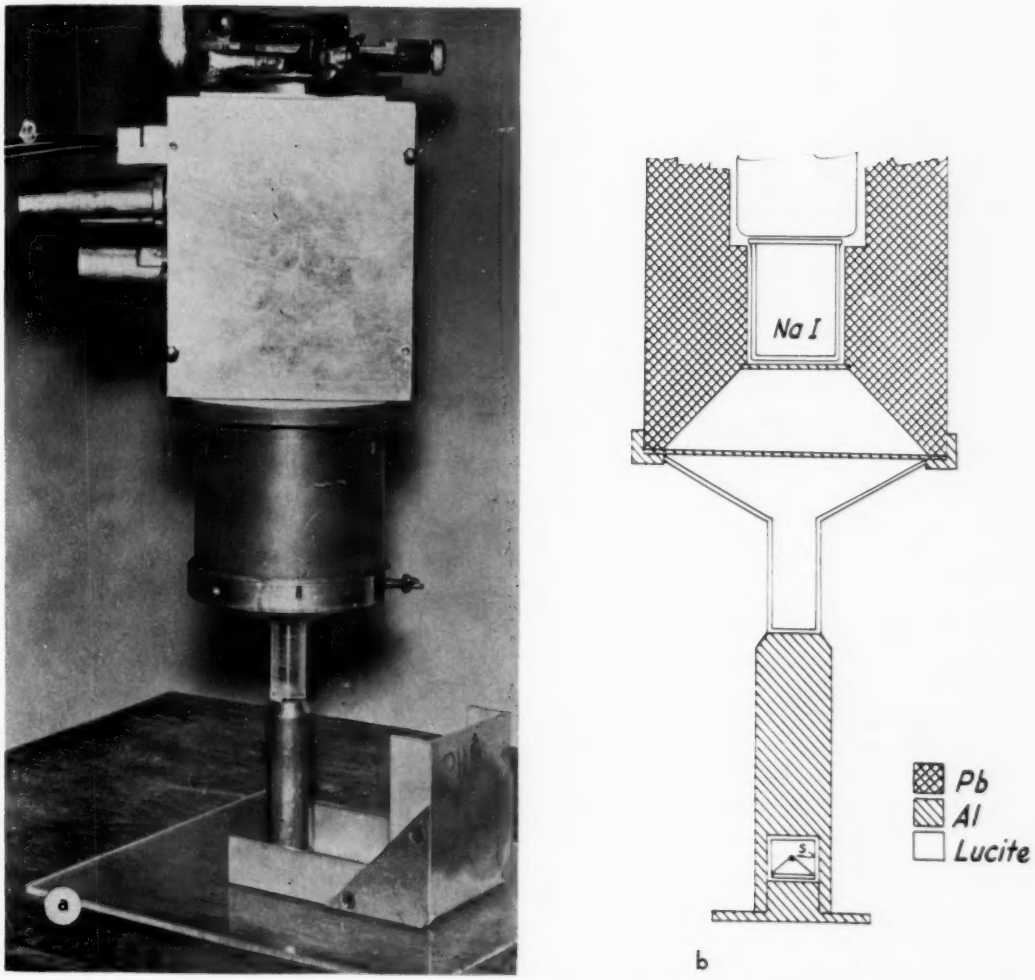

Fig. 5. (*a*) The physical arrangement of Cs^{137}-in-Al source in relation to our detector. (*b*) Diagram of *a*.

the detector can be represented by the dashed curve *a*, shown in Figures 7, 8, 9 and 10. Curve *a* is a pulse spectrum from a Cs^{137} point source taken with 9.1 per cent resolution (ratio of full width at half height to the abscissa at the maximum of the peak). Curve *a* is normalized so that the area under it above 42.5 volts represents 100 pulses.

The calculated effect of the scattered radiation in the detector is shown for a range of scattering masses by the dashed curves *b* to *h*, inclusive, of Figures 7, 8, 9 and 10. These curves show the expected number of pulses per volt pulse height interval due to scattered radiation per 100 total-energy pulses due to unscattered radiation. By the expression "total-energy pulse" is meant a pulse in the detector resulting from conversion of the total photon energy into light and therefore contributing to the peak of curve *a*. To obtain the predicted total pulse spectrum, the ordinates of any one of the curves *b*, *c*, *d*, etc., add directly to the corresponding ordinates of curve *a*.

The curves *b*, *c*, *d*, and *e* of Figure 7 display the calculated trend in the scatter spectrum as the cylinder length is varied keeping R constant at 1.25 inches. The values of L are respectively 1.5, 3.0, 6.0, and 10 inches. The curves *g*, *f*, *d*, and *h* of Figure 8 display the trend as radius and length are varied together, the ratio R/L being kept constant at 0.21. The values of

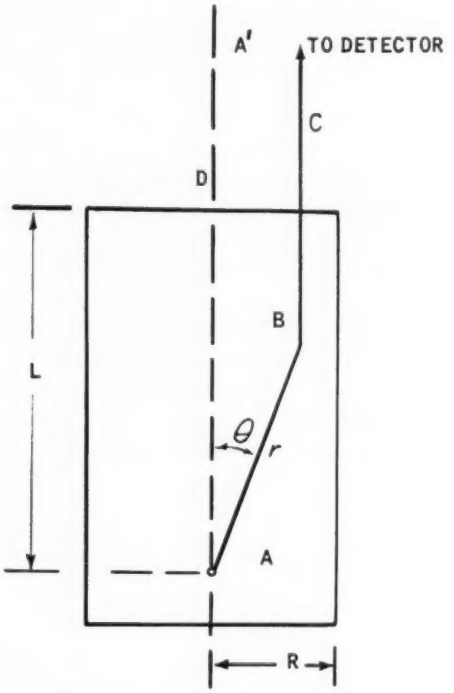

FIG. 6. Diagram of aluminum scattering cylinder with Cs^{137} point source at *A*, showing typical path by which a photon could reach the detector after being Compton scattered through an angle θ.

L are respectively 2.4, 3.5, 6.0, and 9.6 inches—the curve *d* being one of the family of curves in Figure 7. Figures 9 and 10 are comparisons between calculation and experiment. Figure 9 is a plot for the cylinder where $R=1.25$ inches and $L=6$ inches. The solid curve represents the calculated total pulse spectrum. It is the sum of *a* and *d*, which are repeated from previous figures. The circles are experimental points taken with a multichannel analyzer with approximately half volt channels. For comparison are shown (black crosses) the experimental points obtained from an I^{131} sample taken under the same conditions. The I^{131} sample was in the usual clinical form of a 30 ml. water solution of I^{131} salt, since this was the form the Cs^{137} sample was intended to simulate. Figure 10 is similar to Figure 9 except for dimensions of the scatterer. For Figure 10, $L=3.5$ inches and $R=0.75$ inches. The experimental points of Figures 9 and 10 were taken with 9.1 per cent resolution for the Cs^{137} point source. The statistical uncertainties in the experimental points vary from about 6 per cent for the lowest point to less that 3 per cent for the highest.

The calculations evidently furnish a fairly reliable estimate of the amount of scattering to be expected. As indicated by the data of Figures 9 and 10, the calculations underestimate the scattering, as might be expected from neglecting the possibility of more than one large angle scattering per photon. It is clearly not possible with a cylinder of homogeneous scattering material to achieve a concentration of scattered radiation in a small energy interval. This conclusion is especially important with respect to energy intervals close to 660 kev. It is therefore not possible to broaden the total energy peak in an arbitrary manner.

From Figures 7 and 8, it is clear that the

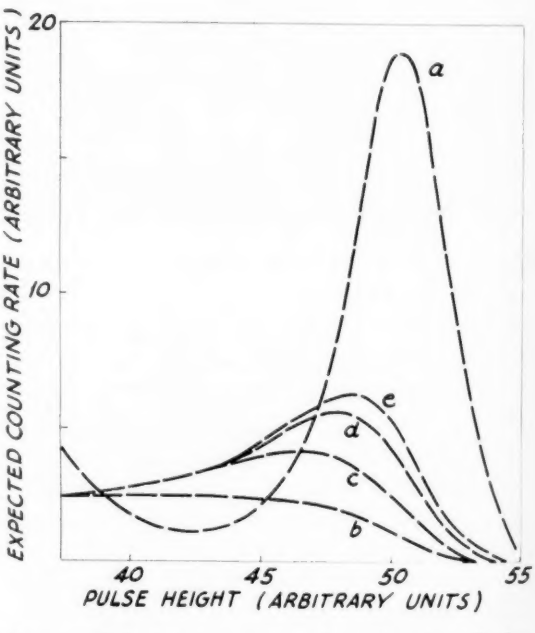

FIG. 7. Calculated spectra of scattered radiation from aluminum cylinders with 1.25 in. *R* and varying lengths: *b*, $L=1.5$ in.; *c*, $L=3.0$ in.; *d*, $L=6.0$ in.; *e*, $L=10$ in. The normalized Cs^{137} point source curve *a* shows the effect of unscattered radiation reaching the detector. The scattered radiation is calculated in all cases for the amount of unscattered radiation given by curve *a*.

intensity of the scattered spectrum increases with increasing mass of scatterer for proportions in which the length is several times the diameter. For a given diameter, the center of gravity of the scattered spectrum tends to higher energy (smaller scattering angle θ) as the length increases, up to a few diameters. However, as illustrated by a comparison of curves *d* and *e* in Figure 7, material far from the source in a very long scatterer contributes relatively little to the spectrum.

It is possible to approximate the I^{131} spectrum fairly well on the low energy side of the peak. This is quite satisfactory for our application, in which the lower and upper biases of the pulse height analyzer are well away from the peak base. The scatterer of Figure 10 somewhat overcompensates since the area under a curve through the I^{131} points would be somewhat greater than the area under one through the Cs^{137}-plus-scatterer points above a suitable lower bias

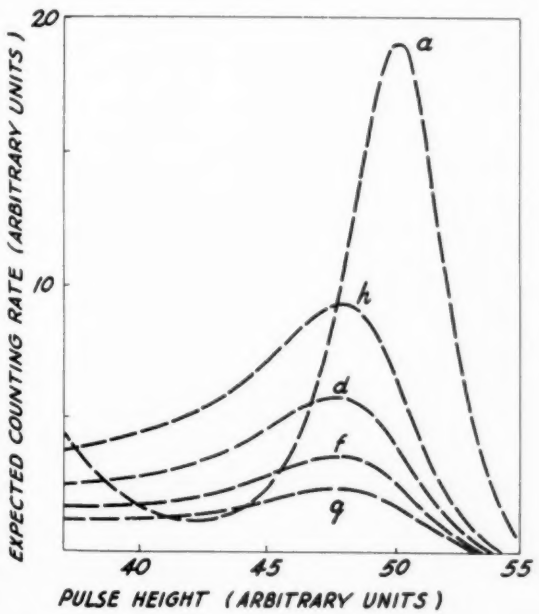

Fig. 8. Same as Figure 7 except that *R* and *L* are varied in constant proportion: *g*, $R=0.50$ in. and $L=2.4$ in.; *f*, $R=0.75$ in. and $L=3.5$ in.; *d*, $R=1.25$ in. and $L=6.0$ in.; *h*, $R=2.0$ in. and $L=9.6$ in. Normalization is to the amount of unscattered radiation reaching the detector shown by curve *a*.

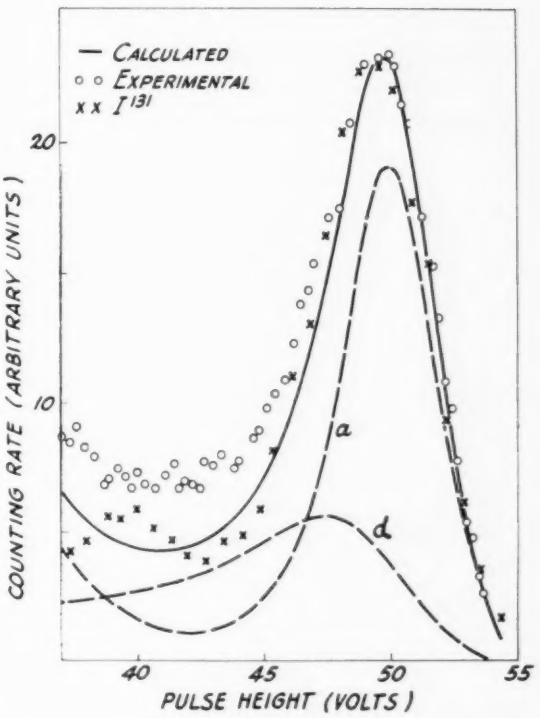

Fig. 9. Comparison of calculated and measured total spectra from a Cs^{137} source in a 1.25 in. $R\times 6$ in. *L* aluminum scatterer. The calculated solid curve is the sum of *a* and *d*. A measured spectrum from I^{131} in 30 ml. water is shown for comparison.

position such as 42.5 volts. The standard we use provides somewhat less than optimum scattering. Final choice of dimensions must depend on data like those of Figure 4, which show relative changes in counting rates of I^{131} and the Cs^{137}-in-Al for small gain and bias variations under otherwise standard operating conditions.

The fact that choice of operating conditions establishes the requirements placed on design of the source has been mentioned. The problem of tailoring the Cs^{137} spectrum to the I^{131} spectrum for clinical standardization can only be attacked after a choice of clinical operating conditions is made. The fact that we have chosen the aluminum dimensions to give a best correspondence between the spectra at 19 volts was governed by our previously made choice of the 19–26 volt interval in the I^{131} spectrum with the peak at 22.5 volts. This choice has some arbitrariness, but it appears to us to mini-

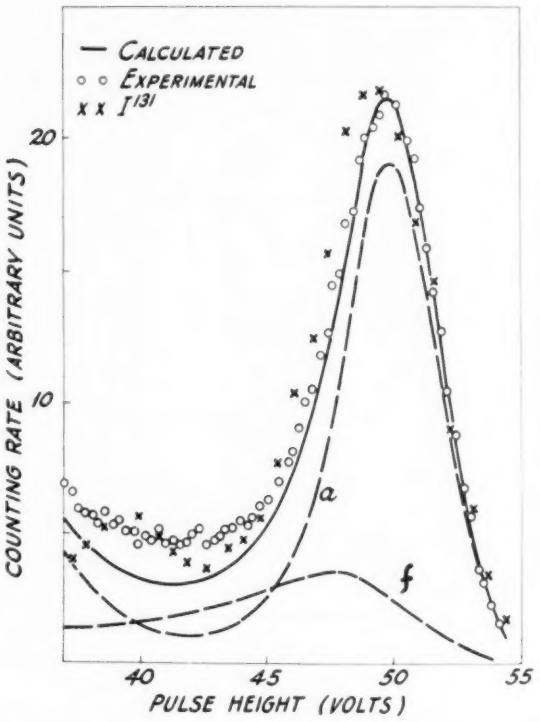

FIG. 10. Same as Figure 9 except that the scattering cylinder dimensions are: $R=0.75$ in. and $L=3.5$ in.

mize the effect on the I^{131} reading of gain and bias variations. Since the upper channel bias rejects relatively few pulses, there is no problem from overload of the anticoincidence circuits, and channel width need not be maintained to high accuracy. The choice of a lower bias at 19 volts minimizes dependence of the counting rate on the lower bias position, as is obvious from inspection of Figures 2 and 3, which show that the lowest point of the I^{131} spectrum occurs here. Possible deterioration of photomultiplier resolution with time makes it desirable to set the lower bias somewhat away from the peak. The peak broadening would thus be felt earlier at 19.5 than at 19.0 volts. The possibility of matching the I^{131} pulse spectrum in this region by introducing scattered radiation in the Cs^{137} standard spectrum strengthens the argument for the choice. It is probably needless to remark that inclusion of the total peak is desirable in order to obtain the best counting rates for the lowest dosages without sacrificing the advantages of pulse height analysis.

RESULTS

Over a period of two years, consistency of measurements within 2 per cent has been obtained on readings of the standard and on readings of I^{131} samples where activities have been accurately determined by established assay procedures. A single Cs^{137}-in-Al standard has been used throughout this period, obviating the expenditure of time in preparing short-lived standards and creating confidence in the long term stability of the measuring procedures. Photomultiplier changes were necessary on the average only once per instrument during this period. When the resistor ratio $r_2/(r_2+r_1)$ was readjusted to bring the I^{131} and Cs^{137}-in-Al peaks into coincidence after these replacements, recalibration with sufficient statistical accuracy showed that the counting rate from the Cs^{137}-in-Al had remained within 1 per cent of the value observed prior to replacement. Further observations after replacement have always confirmed constancy of this value. Thus the results justify the amount of effort expended in the initial calibration. Investigation of instrument performance when the standard value deviates from the accepted value consistently by 2 per cent has always indicated malfunction in the gain and bias circuits which was undetected by conventional methods.

A further advantage has been the ability to assess changes in millicurie value when dealing infrequently with large amounts of I^{131}. When the analyzer amplifier system is in good operative condition, amounts of I^{131} varying from 2 microcuries to 7 millicuries may be counted using lead absorbers. Minor electronic changes which cause a shift in millicurie value may occur, but are readily detectable by the use of the long-lived standard. Thus, shifts in millicurie value observed on any particular amount of I^{131} may be traced to either electronic malfunction or true error in dose preparation.

This paper has been written with the

conviction that simplification of calibration, maintenance and measurement techniques are an important and too often neglected aspect of the introduction of new equipment and methods into medical clinics and laboratories. We believe that some of the details of this procedure represent time-saving simplifications of current methods.

SUMMARY

Simple and accurate methods for calibrating and maintaining the accuracy of equipment using pulse height analysis for clinical I^{131} measurements have been worked out. Complicated procedures involving knowledge of electronics and nuclear physics were avoided.

The most important detail involved the use of a long-lived Cs^{137} standard which was made to simulate the characteristics of I^{131} by: (1) installation of a resistor set and switch in the linear amplifier such that superimposition of the cesium and iodine curve occurs; and (2) modification of the Cs^{137} pulse spectrum by limited use of Compton scattering in an aluminum shield.

Over a period greater than two years, consistency of measurements within 2 per cent has been obtained.

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THE SYNDROME OF EXOPHTHALMOS, HYPERTROPHIC OSTEOARTHROPATHY, AND PRETIBIAL MYXEDEMA

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THIS is a report of an adult Negro female who developed hypertrophic osteoarthropathy and pretibial myxedema following I^{131} induced remission of an exophthalmic goiter.

REPORT OF A CASE

The patient, a fifty-three year old Negro female, had noted the onset of easy fatigability, heat intolerance, and persistent night sweats about three years prior to her present admission to the hospital. She had also noted some weight loss at that time in spite of an increase in appetite. The thyroid was enlarged, smooth, and firm. There was bilateral exophthalmos. The palms of her hands were moist and there was a definite tremor. The blood cholesterol was 175 mg. per cent (normal 140–240 mg. per cent), protein bound iodine was 10.5 μg. per cent (normal 4–8 μg. per cent), and radioactive iodine uptake was 67 per cent (normal 17–37 per cent).

She was given 7 mc I^{131} and, over the next year, gained approximately 23 pounds and felt less nervous. The blood cholesterol rose to 282 mg. per cent and the protein bound iodine fell to 1.7 μg. per cent. The radioactive iodine uptake was recorded as 4 per cent. The clinical impression was hypothyroidism and she was placed on 1.5 gr. of thyroid extract per day. In spite of the thyroid therapy her hypothyroid state persisted

FIG. 1. Photograph showing the degree of exophthalmos present after thyroid therapy over a period of approximately two years.

FIG. 2. Photograph showing swollen hands and fingers.

FIG. 3. Photograph showing thickened and wrinkled skin, particularly about the anterior aspect of the ankles.

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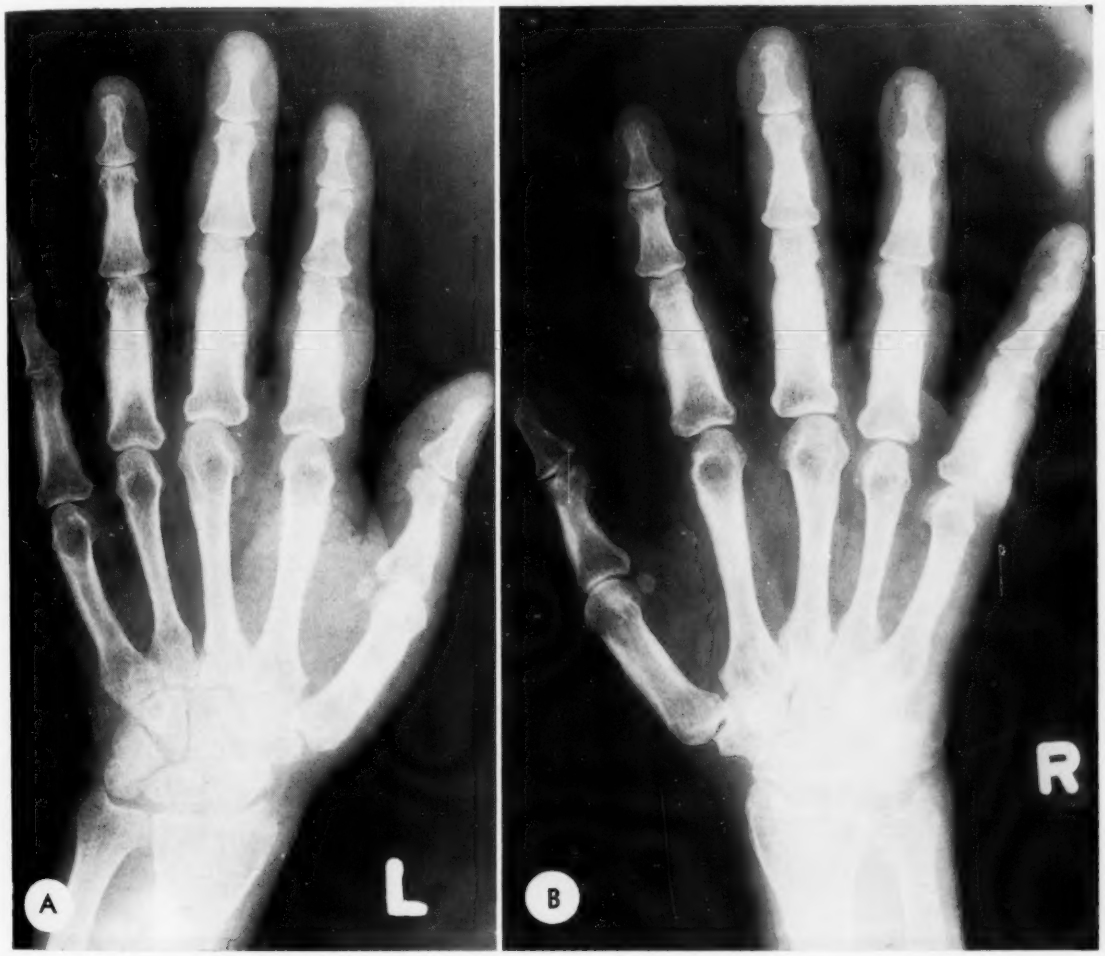

Fig. 4. (*A* and *B*) Roentgenograms of the hands showing diffuse, symmetric, periosteal new bone formation about the shafts of the proximal phalanges and both first metacarpals. Compare *A* with Figure 5.

over the next two years with the gradual development of progressive swelling of her hands, legs, and ankles.

With this history, the patient was admitted to the hospital where a skin biopsy from her left ankle was interpreted as showing changes compatible with myxedema. The basal metabolic rate was minus 12 per cent and the radioactive iodine uptake was 6 per cent. Exophthalmometric records had shown progressive increase in the degree of her exophthalmos. Figure 1 is a photograph taken on this admission. Other pertinent physical findings were swollen but nontender hands and fingers (Fig. 2). The skin of the legs, particularly about the anterior aspect of the ankles, was thickened and wrinkled (Fig. 3).

Roentgenograms of the hands (Fig. 4, *A* and *B*) showed diffuse, symmetric, periosteal new bone formation about the shafts of the proximal phalanges and both first metacarpals. We were fortunate in having an earlier roentgenogram of the patient's left hand (Fig. 5) which showed normal osseous structures four years earlier. In the feet (Fig. 6) the same, very symmetric, periosteal new bone development was seen in the first metatarsals bilaterally and, to a lesser extent, in the other metatarsals. The phalanges showed only minimal involvement. A chest roentgenogram showed no mediastinal or pulmonary pathology except for chronic fibrocalcific disease in the left upper lobe.

DISCUSSION

Hypertrophic osteoarthropathy was first described as an ossifying periostitis by

FIG. 5. Roentgenogram of the left hand, made four years before Figure 4*A*, showing normal osseous structures.

Bamberger in 1889. This condition is usually characterized by clubbing of the fingers and toes, an unusual nonpitting edema of the distal portions of the extremities, and subperiosteal proliferation of bone. Hitherto this condition has been described as being secondary to suppurative intrathoracic lesions, mediastinal new growths, tumors of the lung, abscess of the liver, pyelonephritis, cirrhosis of the liver with jaundice, certain obstructive lesions of the gastrointestinal tract, possibly syphilis, and perhaps congenital heart disease. In some cases the condition has been described as characterized by the absence of a discoverable primary disease and by the tendency for this syndrome to have a familial occurrence. Thus, hypertrophic osteoarthropathy is seen in association with a wide variety of primary diseases but it has only rarely been observed with diseases of the thyroid. There is no single hypothesis that adequately explains the syndrome.

The new bone is confined to portions of the skeleton which are covered by periosteum and is not seen in the joints, although involvement of the end of the bone may lead to disability in the joint itself. The change in the bone consists of a deposition of new bone between the cortex and the periosteum, particularly in the lower ends of the bones of the forearm and the lower leg and in the metacarpal and metatarsal bones. In extreme cases, similar changes have been described in the clavicles, ribs, pelvic bones, scapulae, malar bones, and even in the transverse processes of the vertebrae. Histologically, the cortical part of the bone shows little if any change. One extraordinary feature of the syndrome is the symmetry of the process, with the same portions of the same bones of the two hands involved to approximately the same degree.

Danforth and Humphrey[2] recently reported a case of a forty-six year old Negro male treated for hyperthyroidism with 12 mc of I^{131}. One year later he noted swelling of his legs with thickening and hardening of the skin in the pretibial region. A biopsy of this area of the skin was typical of pretibial myxedema. Roentgenograms showed minimal periosteal new bone formation involving several metacarpals and proximal phalanges bilaterally. Greene[5] described a seventy-four year old male who was treated eighteen years previously with potassium iodide for exophthalmic goiter. The goiter disappeared with the iodide therapy but about fifteen years later his eyes became prominent and he developed a remarkable degree of clubbing of the fingers. There was also some pretibial thickening of the skin regarded as possible pretibial myxedema. Roentgenograms of the hands revealed subperiosteal new bone formation along the shafts of the phalanges and metacarpals. Additional similar cases following subtotal thyroidectomy have been described by Thomas,[7] Diamond,[3] and Rynearson and Sacasa.[6]

Fig. 6. Roentgenograms of the feet demonstrating symmetric, periosteal new bone development in the metatarsals, especially obvious in the first metatarsals.

Camp and Scanlan[1] presented 5 cases of hypertrophic osteoarthropathy without apparently known cause. One of these cases is similar to that presented in this article in that the patient developed myxedema and exophthalmos with massive enlargement of all the bones of the extremities due to subperiosteal proliferation in the diaphyseal portions.

Findlay and Oosthuizen[4] described a condition known as the syndrome of pachydermoperiostosis, in which thick furrowed skin is found particularly on the forehead, upper eyelids, and palms and is associated with hyperostosis. These authors describe this condition as a specific entity and attempt to differentiate it from thyroid osteoarthropathy.

SUMMARY

The occurrence of hypertrophic osteoarthropathy in association with exophthalmos and pretibial myxedema forms a rare syndrome of treated hyperthyroidism. These findings apparently have no rational explanation as regards thyroid function,

although they usually become evident during a hypothyroid state following treatment of the hyperthyroidism. The present article is apparently the second reported case of this syndrome following remission of an exophthalmic goiter after I^{131} therapy. Other similar cases have been reported following subtotal thyroidectomy and potassium iodide administration.

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THE EXCRETION OF RADIOACTIVE IODIPAMIDE (CHOLOGRAFIN) BY NORMAL AND CIRRHOTIC MALES*

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SINCE the introduction of iodipamide (cholografin) as an intravenous cholangiographic agent,[2] it has been observed that in the presence of chronic hepatic disease the contrast medium is excreted through the kidneys rather than through the liver and biliary passages.[1,2,6] The introduction of cholografin labelled with I^{121} has made available an easily detectable form of the medium. Using this preparation, attempts have been made to measure quantitatively the excretion of radioactive cholografin in humans and animals with normal and abnormal liver function.[3,4,5,7] This study compares the excretion of radioactive cholografin by cirrhotics and patients with apparently normal hepatic function.

MATERIAL AND METHODS

Thirty-seven male patients at the Philadelphia Veterans Administration Hospital were studied. Twenty-two of these had normal hepatic function as measured by the usual screening tests. The remaining 15 were diagnosed as having cirrhosis of the liver by the appropriate clinical and laboratory criteria and/or by liver biopsy (Table II).

Cholografin labelled with I^{131} of very high specific activity (average about 1 mc/ml.) was obtained from a commercial supplier† and was used throughout the study. From each new purchase an assay for specific activity was done. Exactly 10 μc of the solution was diluted with sterile physiologic saline solution to a volume of 12 ml. Ten milliliters of this solution (containing about 8 μc of radiocholografin) were injected intravenously into patients who had been previously fasted for about eight hours.

The patients were studied by several means, including serial serum radioactivity determinations, 2 hour fractional and 24 hour fractional and 24 hour urinary radioactivity determinations, and by external counting over the liver and thyroid in some patients. The urine of several patients was also studied at 48 and 72 hours.

As a standard, 1 ml. of the original solution as diluted and prepared for injection was further diluted to 100 ml. in water, and a 2 ml. aliquot of this dilute solution was assayed for radioactivity by being placed in a crystal well counter and assayed for a sufficient length of time to give a ± 3 per cent standard counting variation error (5 to 10 minutes), using a single channel gamma-ray scintillation spectrometer. The urine samples were assayed by similarly counting a 2 ml. sample of the urine specimen, and the percentage excretion was obtained by use of the following formula:

$$\% \text{ excretion} = \frac{\text{cpm (2 ml. urine)} \times \text{vol. of urine}}{\text{cpm (2 ml. of standard)} \times 10}$$

Serum radioactivity was obtained by assaying 2 ml. of serum in a similar manner. External counting over the liver and thyroid was done by the usual techniques used for the latter and, in the case of the liver, by centering the tube over a point halfway between the midclavicular and anterior

† Supplied by E. R. Squibb & Sons (Division of the Olin Mathieson Chemical Corporation).

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Table I

COMPARISON OF URINARY EXCRETION OF RADIOACTIVE CHOLOGRAFIN IN NORMAL INDIVIDUALS AND CIRRHOTICS

	24 Hour Urinary Excretion of Radioactive Cholografin (per cent of total)		
	<12%	12–14%	>14%
Cirrhotics	3 (20%)	2 (13%)	10 (67%)
Normals	16 (72%)	3 (14%)	3 (14%)

axillary lines, 5 cm. below the top of the liver as determined by percussion.

RESULTS

We were unable to demonstrate any significant difference between the normal subjects and the cirrhotics in the level of serum radioactivity, the rate of change of this level, or in the external counts over the liver, and these methods were therefore abandoned after the first few subjects were so studied. There was, however, a difference between the groups both in the rate of urinary excretion and the total 24 hour urinary excretion. These results are summarized in Tables I, II and III and in Figure 1. Three of the cirrhotics, or 20 per cent, had 24 hour excretions of radioactive cholografin of less than 12 per cent, while 16 of the normals, or 72 per cent, fell below this level. Two, or 13 per cent, of the cirrhotics and 3, or 14 per cent, of the normals fell into a 12 to 14 per cent range. Finally, 10, or 67 per cent, of the cirrhotics and 3, or 14 per cent, of the normals were above 14 per cent. The highest value in a normal patient was 18.9 per cent, while values for cirrhotics ranged up to 45 per cent in this study. There was detectable activity over the thyroid in all patients studied for such activity.

DISCUSSION

The accurate measurement of 2 hour fractional urine samples required the insertion of an indwelling bladder catheter with the attendant discomfort to the subject, danger of infection and added burden to the nursing personnel. We, therefore, felt that a single 24 hour collection would be preferable if the results corresponded. This proved to be the case (Fig. 1).

The presence of countable radiation over the thyroid gland indicates that in the

Table II

LABORATORY DATA AND CHOLOGRAFIN EXCRETION IN 15 PATIENTS WITH CIRRHOSIS OF THE LIVER

Patient	Age	BSP Retention* (per cent)	Alkaline Phosphatase (Shinawara units)	Bilirubin (mg./100 ml.)	Tissue Diagnosis	24 Hour Urinary Radioactive Cholografin (per cent of total)
S.R.	46	63	12.0	38.6	No	17.2
V.I.	43	26.5	14.8	4.7	Yes	19.5
E.R.	37	43	11.1	4.3	Yes	24.0
C.D.	36	37.5	11.7	30.6	No	15.3
J.M.	61	37.5	9.2		Yes	9.0
J.L.	45	23		2.9	No	14.4
P.L.	51	37.5	4.9	0.9	No	8.0
B.P.	39	30	19.9	2.2	No	15.9
C.T.	44	22	12	1.4	No	5.0
J.B.	56	26.5	7.1		No	45.0
J.S.	36	38.5	5.9	4.4	No	14.7
S.B.	44	31	16.5	1.0	Yes	19.3
S.R.	53	42	10.2	5.3	Yes	34.7
M.K.	62	33	7.7	2.7	No	13.0
B.H.	33	25.5	7.9	1.4	Yes	12.3

* Using 5 mg. per kg. of body weight and checking retention after 45 minutes.

TABLE III

LABORATORY AND CLINICAL DATA ON 6 OUT OF 22 PATIENTS WITH APPARENTLY NORMAL HEPATIC FUNCTION WHO HAD ELEVATED 24 HOUR RADIOACTIVE CHOLOGRAFIN EXCRETION

Patient	Age	24 Hour Urinary Radioactive Cholografin (per cent of total)	Laboratory and Clinical Data
C.L.	46	18.7	BSP, alkaline phosphatase normal; convalescent myocardial infarction
E.T.	59	13	BSP normal; rheumatic heart disease, congestive failure
T.K.	38	14	BSP, alkaline phosphatase, bilirubin normal; acute pancreatitis, alcoholism
E.A.	46	14.1	Alkaline phosphatase normal; coronary insufficiency
R.S.	44	18	BSP, alkaline phosphatase normal; erythema multiforme; steroid therapy
W.H.	37	13.1	Alkaline phosphatase normal; atopic dermatitis; steroid therapy

material as prepared there is a definite amount of free I^{131} available to the gland. No quantitative estimates of this were made.

Due to the high specific activity of the compound used, the dose of cholografin employed was less than that used for skin testing for sensitivity prior to gallbladder roentgenography. One would, therefore, not expect to see sensitivity reactions in the use of this amount of contrast material.

The results obtained confirm the fact that, in the presence of hepatic disease, radioactive cholografin is excreted through

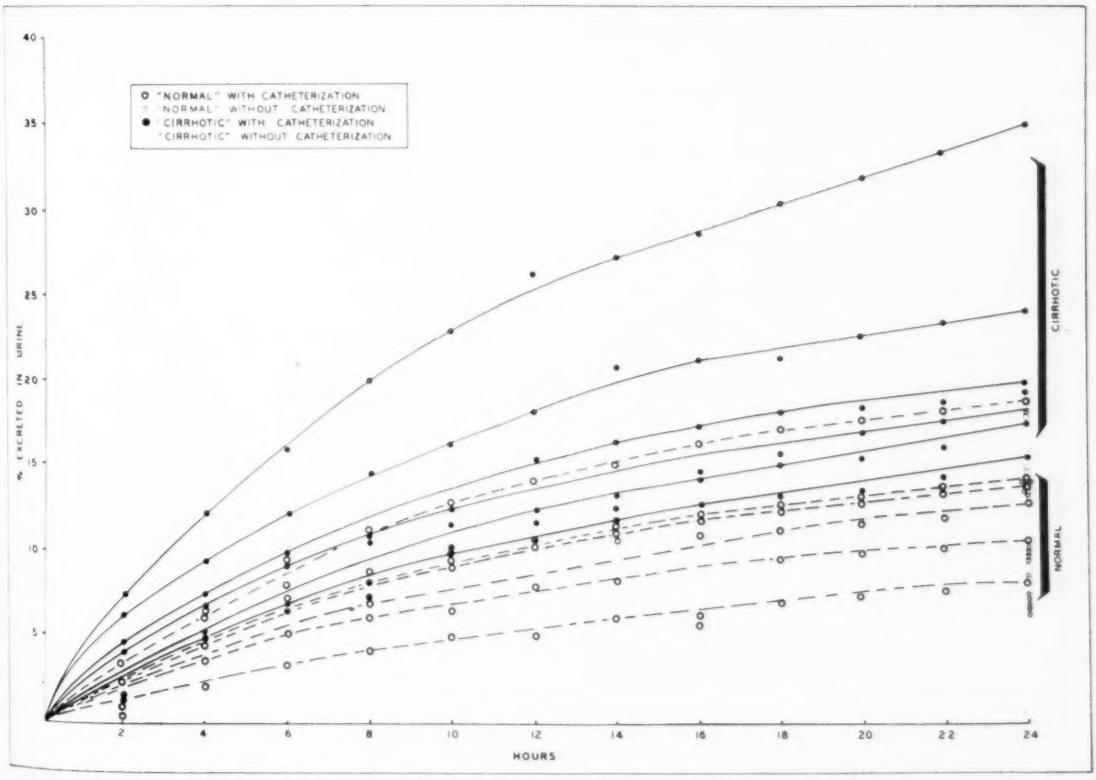

FIG. 1. Graph showing excretion of radioactive cholografin in normal and cirrhotic males.

the kidneys rather than through the liver and biliary passages.

CONCLUSIONS

Cholografin labelled with I^{131} injected intravenously into 37 normal and cirrhotic subjects gave urinary excretions differing significantly between both groups, both in total excretion and in rate of excretion. With few exceptions cirrhotics excreted a larger percentage of the contrast material in 24 hours and at a more rapid rate than normals. The total excretion and rate of excretion mirrored each other in all cases. Study of the urinary excretion of radioactive cholografin at the end of 48 and 72 hours yielded no information additional to that already obtained

There was detectable radioactivity over the thyroid gland in all patients so studied. Counting of blood samples and external counting over the liver failed to differentiate between the two groups.

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SCINTISCANNING OF DOG KIDNEYS USING DIODRAST I^{131}*

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METHODS for delineating renal parenchymal defects caused by neoplasm or cyst using intravenous pyelography or angiography reveal secondary distortion in either calyceal appearance or vascular distribution after the tumor has reached sufficient size. It would be highly desirable to define the presence of a small renal tumor before such secondary manifestations appear. Because scanning methods using I^{131} have proved of great value in the diagnosis of nonfunctioning thyroid lesions such as adenoma, carcinoma or colloid cyst, an effort has been made to apply to renal scanning the same principles used in thyroid scanning. This paper is a report of an initial study carried out in dogs wherein the goals were: (1) to delineate renal tissue by scanning after administration of I^{131} labeled iodopyracet (diodrast), (2) to determine the body retention of this radioactive material and to calculate therefrom the radiation dosage to the whole body and blood, and (3) to determine if significant changes in blood count or body tissues would occur following the administration of radioactive material.

METHOD AND MATERIAL

Scanning Method. Sterile diodrast I^{131}† having a specific activity of approximately 10 mg. per 1 mc (range 1.5 to 16 mg.) was injected rapidly and undiluted into the tubing through which an infusion of 5 per cent dextrose in water was running. A tuberculin type syringe was used to measure and administer the material. The infusion was maintained at approximately 20 to 30 drops per minute throughout the study to permit rapid repeat intravenous injections.

In two preliminary studies, an injection of 1.4 gm. (4 cc. of 35 per cent solution) of stable diodrast was given prior to injection of diodrast I^{131} to try to retard excretion of I^{131} labeled dye and thus to maintain longer and better renal I^{131} concentration for scanning. Scans following this technique were unsatisfactory because concentration of I^{131} sufficient for scanning was not attained in the renal area at any time in a two hour period following injection of stable diodrast.

Ten mongrel dogs were given potassium iodide in their drinking water 2 days and 1 day prior to the study. Anesthesia with veterinary nembutal was maintained throughout the study period to assure accuracy and constancy of positioning. Scanning in the prone position was performed with a 1 inch by 1 inch sodium iodide (Th) scintillation crystal with collimation as described by Allen and Risser[1] using a motor driven constant speed scanner with print-out recording of I^{131} 364 kev. gamma ray defined by a research grade pulse height analyzer and linear amplifier.

In early studies the kidney was traversed by scans 5 mm. apart, and recording was made by a 2 mm. wide printing stylus. In later studies a 5 mm. printing stylus was used with the same 5 mm. scan spacing factor. Duration of scan of each kidney varied from 4 to 12 minutes and of the complete study from 10 to 21 minutes, depending on the speed setting of the motor drive. With settings of 0.45 cm./sec. scan speed, good definition was obtained in the scan. The scan of a single kidney was begun within one minute of injection of 100 to 200

† Obtained from Abbott Laboratories, Oak Ridge, Tennessee.

* From the Radioisotope, Radiology and Laboratory Services of the Veterans Administration Hospital, and the Department of Physics, The Rice Institute, Houston, Texas.

μc diodrast I^{131}. A second injection was made at the finish of scan of this kidney and immediately prior to the beginning of scan of the opposite kidney. Occasionally a third injection was required to maintain I^{131} concentration in the renal area. This technique was found more satisfactory than an earlier procedure of injecting a single large dose. In these early scanning trials with a single large dose, concentration of I^{131} had decreased to such degree that poor definition of renal outline was obtained in the areas scanned at 10 to 20 minutes after injection.

It is important, as in scanning other organs, that careful attention be paid in advance to peak location of the 364 kev. I^{131} gamma ray in the pulse height analyzer channel, and to speed, spacing and limits of area to be covered by the scan. Settings must be made in advance of actual performance of the scan, since the time of satisfactory recording is limited by rapid excretion[4] of the I^{131} labeled dye. Also, we found it useful to give a preliminary 20 to 25 μc dose for purposes of gross kidney location and of finding spacing and limit settings on the scanning controls. The total dosage, including the preliminary dose for completed satisfactory scans, ranged from 136 to 464 μc.

Assay Procedures. Eight adult mongrel dogs with preparation of potassium iodide in drinking water for 2 days prior to test and additional subcutaneous injection on the day prior to test received 340 to 400 μc diodrast I^{131} intravenously (using a foreleg vein). Radioassay and survey of body retention was performed in the following manner:

(1) Five cc. of blood was withdrawn from an external jugular vein at 30 minutes, 2 hours, 4 hours, 6 hours, 1 day, 2 days, 3 days, 5 or 6 days after injection. Radioactivity counting was done in a calibrated Texas well Geiger-Müller counter. Calculation of the radioactivity remaining in the total blood volume (estimated at 65 cc./kg. body weight) was made and the per cent of injected dose retained at each time was plotted on linear graph paper.

(2) Urine and feces were collected and assayed by aliquot removal; the total radioactivity excreted was calculated as the per cent of dose injected. These collections were continued for one week after injection.

In addition, 4 dogs with similar preparation received 400 μc diodrast I^{131} subcutaneously, and similar blood, urine and fecal studies were performed.

Blood and Tissue Studies. Four animals received 400 μc intravenously and serial studies of hematocrit, white blood cells and platelets were performed[5] up to 7 to 25 days following injection. All animals used for scanning studies were sacrificed at from 4 to 8 weeks following the study and tissues were examined grossly. Sections of thyroid, heart, lung, liver, spleen, pancreas, kidneys, urinary bladder and bone marrow were fixed with 10 per cent neutral formalin and examined microscopically after suitable fixation and staining with hematoxylin and eosin.

RESULTS

Scanning. Figure 1 is a scan of one of the animals. For this scan two doses of diodrast I^{131} (without preliminary stable diodrast injection) were given rapidly, the size of each dose being 105 μc. As soon as the scan of the left side was completed or nearing completion, the second dose was administered. A gross outline of renal parenchyma can be seen in the completed scan (Fig. 1). The time required for dose injection and scanning was 17 minutes. Similar results were obtained with this multiple dose split-scanning technique in 5 additional dogs. High vascular radioactivity was also seen in these scans, and the lower portion of liver and gallbladder was partially outlined when the scan was continued over the right upper flank.

Assay. Table 1 shows the per cent of injected I^{131} retained in the estimated total blood volume (based on body weight) in the dogs injected intravenously or subcutaneously with 139 to 400 μc diodrast

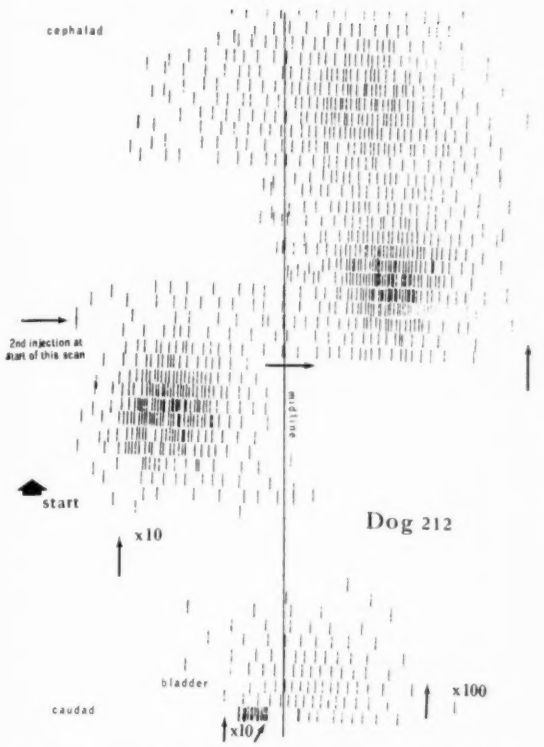

Fig. 1. Scan of renal areas performed as described in the text using two intravenous doses of diodrast I^{131} of 105 μc each. Both renal areas as well as liver and gallbladder areas are outlined by this technique. High background due to vascular content of radioactivity is apparent. A scaling factor of 10, as indicated, was used in the renal and hepatic areas; a factor of 100, as indicated, was used in the region of the bladder, where scanning was finally terminated.

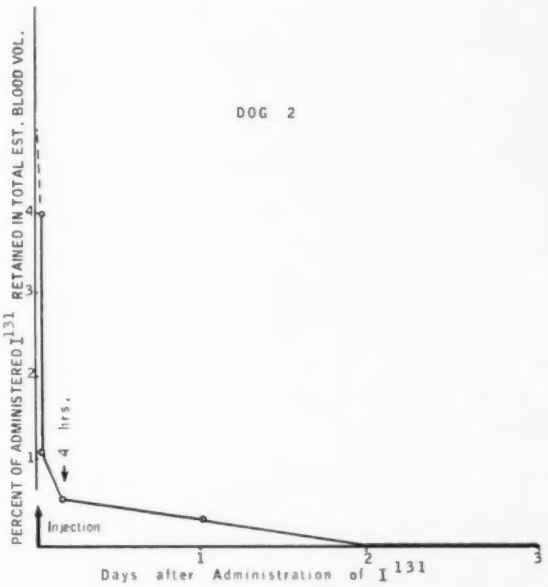

Fig. 2. Per cent retention of radioactivity in total estimated blood volume is shown in relation to time following intravenous injection of 340 μc I^{131} labeled diodrast.

I^{131}. As anticipated on the basis of previous data,[4] a rapid decrease in blood radioactivity was seen in those injected intravenously. In animals injected subcutaneously the radioactivity at 30 minutes was appreciable and fell rapidly thereafter, although minute amounts were still detectable as long as 96 hours after injection. The per cent of dose excreted in urine and feces in these animals in the week following injection ranged from 81 to 103 per cent, the major portion being excreted in the first 24 hours following injection. By linear graphing (Fig. 2) of the results of blood radioactivity assay, and measurement of the area under the curve throughout the first 24 hours, a calculation of rad dosage was made according to the method outlined by Quimby.[3] In the case of dog No. 9 (which retained the greatest amount in the series) 178 mrad/mc was delivered to the whole body. Dog No. 5 retained the smallest amount throughout the first 24 hours and was calculated to have received 25 mrad/mc whole body radiation exposure. Bone marrow and blood dosage is estimated to be two-thirds of the body value.[3]

Blood and Tissue Studies. Blood cell counts showed no significant change in animals studied for 7 to 25 days after injection. Microscopic examination of the various organs revealed no pathologic alterations in animals sacrificed up to 40 days.

DISCUSSION

On the basis of data from these studies, it appears feasible to attempt renal scanning in humans. This conclusion is based on the following considerations:

(1) If a large enough dose of diodrast I^{131} is administered, renal concentration of the I^{131} labeled dye remains sufficiently high for the period required to scan the renal area. Repeat doses may be utilized to

TABLE I

PER CENT OF INJECTED DOSE RETAINED IN TOTAL BLOOD VOLUME (ESTIMATED) FOLLOWING ADMINISTRATION OF DIODRAST I^{131} INTRAVENOUSLY OR SUBCUTANEOUSLY

Time after Injection (hr.)	Dog No. 1	2	3	4	5	6	7	8	9	10	11	12
	Route											
	I.V.	I.V.	I.V.	I.V.	I.V.	I.V.	I.V.	I.V.	S.C.	S.C.	S.C.	S.C.
	Dose (μc)											
	139	340	340	340	400	400	400	400	400	400	400	400
½	3.80	3.98	1.70	2.00	—	4.10	4.20	5.70	3.60	1.80	1.10	2.90
1	0.81	1.20	0.50	0.30	1.50	—	—	—	—	—	—	—
2	—	—	—	—	0.30	0.99	0.85	0.88	—	—	—	—
4	0.42	0.56	0.24	0.24	0.23	0.37	0.38	0.29	0.65	0.36	0.27	0.50
6	—	—	—	—	0.18	0.27	0.26	0.22	0.30	0.44	0.21	0.34
8	—	—	—	—	—	—	—	—	0.39	0.31	0.23	0.17
24	0.15	0.30	0.20	0.10	0.10	0.18	0.32	0.19	0.23	0.21	0.07	0.18
48	Bgnd	Bgnd	Bgnd	Bgnd	0.05	0.13	0.17	0.10	0.40	0.26	0.24	0.13
72	Bgnd	Bgnd	Bgnd	Bgnd	0.03	0.09	Bgnd	0.08	—	—	—	—
96	—	—	—	—	—	—	—	—	0.15	0.16	0.08	0.11
120	Bgnd	Bgnd	Bgnd	Bgnd	—	—	—	—	0.07	Bgnd	Bgnd	Bgnd
144					Bgnd	Bgnd	Bgnd	Bgnd	Bgnd	Bgnd	Bgnd	Bgnd

I.V. = intravenous.
S.C. = subcutaneous.
Bgnd = background.

maintain this concentration. Difficulties due to protein binding (occurring with a low stable diodrast content), as described by Block *et al.*,[2] do not occur with this high dosage, since the specific activity of available material is about 10 mg./mc. Total doses of the order of 2 to 2.5 mc probably will be required for a satisfactory scan in humans and, in this amount, the effect of protein binding will not be observable.

(2) When 2 to 2.5 mc I^{131} as diodrast is used, safety with regard to radiation damage to whole body and blood (including bone marrow) can be assumed, since total body exposure in the first 24 hours of 178 mrad/mc occurred in the dog with the maximal retention and usual values were in the range of 110 mrad/mc. Radiation dosage from intravenous pyelography or angiography may contribute as much or more radiation exposure[6] in the course of screening renal function or diagnosis of vascular or collecting abnormalities of the kidneys. In the case of intravenous pyelography with four anterior position exposures, up to 480 mr is calculated as the midplane tissue dose and 160 mr as the mean marrow dose. Renal scanning in humans with 2 to 2.5 mc should cause no more than 150 mrad exposure to marrow.

It should be possible, therefore, to scan individuals suspected of renal tumors in whom changes in intravenous pyelography appearances have not yet occurred. Thus, diagnostic information may be offered before secondary distortion and probable invasion of the collecting system or major vessels have developed. Furthermore, the method represents no technical hazard to the individual such as those occasionally encountered with angiography. No iodide sensitivity reactions are anticipated following intravenous injection, since amounts of stable diodrast injected are of the order

of 20 to 25 μg. in contrast to routine intravenous pyelography using 10 gm. diodrast, 15 gm. sodium diatrizoate (hypaque), or 15 gm. methylglucamine diatrizoate (renografin), all of which have iodine contents ranging from 59.9 per cent to 62.5 per cent. The preparation of the patient will require, however, prior thyroid blocking with Lugol's solution or tapazole to prevent the thyroid concentration of iodide I^{131} released from the labeled dye.

CONCLUSIONS

Scintiscanning of the kidneys of normal dogs was performed by use of 135 to 465 μc diodrast I^{131} administered intravenously in divided doses during the scanning procedure.

Radioassay procedures based on blood retention of radioactivity revealed a total body radiation exposure during the first 24 hours of 178 mrad/mc in the dog with the greatest blood retention. Excretion studies revealed nearly complete elimination of the administered radioactivity within 3 days, the major portion occurring in the first 24 hours.

No adverse effects on peripheral blood count or on tissues examined after autopsy could be found in animals given 400 μc diodrast I^{131} intravenously or subcutaneously.

The method appears to be feasible for human application where doses of the order of 2 to 2.5 mc are anticipated and where thyroid blockage of I^{131} uptake will be necessary.

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STAINING WITH I^{131} LABELED 4-IODOALIZARIN 3-SULFONIC ACID *IN VIVO*, A TRACER FOR GROWTH AREAS IN BONE*

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ALIZARIN is a well known[1–4] vital staining agent for new bone formation, especially in mammals. The staining of malignant new bone formation *in vivo* in humans was described for the first time by Schorr *et al.*[7] This study gave the stimulus for further experimental investigations in order to prepare a radioactive iodoalizarinate substance for eventual diagnostic and therapeutic effects in malignant bone conditions. The use of iodine derivatives of alizarin was suggested as a contrast medium for diagnostic roentgenography and as a radioactive tracer and a therapeutic agent. The purpose of this study is to evaluate the application of I^{131} labeled alizarin as a tracer and to determine the distribution of iodoalizarin in various organs and tissues.

METHOD OF STUDY

I^{131} labeled 4-iodoalizarin 3-sulfonic acid has been synthesized according to the method developed by Frankel and Moses.[5] A 0.05–1.0 per cent solution at various specific activities (μc per cc.) was injected intraperitoneally or intravenously into young white rats. (For practical purposes no difference was found between intraperitoneal and intravenous routes.) The rats were sacrificed at predetermined intervals and the specific activities in various organs were measured. The radioassay was performed on fresh tissues counted in a well type sodium iodide crystal scintillation counter.

Duplicate samples of the tissues examined were weighed and subsequently counted at a counting efficiency of 28 per cent. The organs which were investigated in this study included liver, spleen, thyroid and kidneys as well as samples of blood, brain, lungs and muscle. Of the bony tissues, the following were examined: the shafts and ends of femur and tibia, the skull, incisors and vertebrae. The determination of the specific activity (in μc per gm. of whole tissue) enabled us to follow the distribution of iodoalizarin in the organism. The results are presented below, either as specific activities (μc per gm. tissue), or as relative activity to blood (*i.e.*, the ratio of the specific activity in the respective tissue to the specific activity in the blood).

RESULTS

The relative distribution of 4-iodoalizarin 3-sulfonic acid (IASA) in various tissues is presented in Table 1. The data of this table are compiled from distribution determinations done on 32 young rats (50–80 gm.).

From the data given in Table 1 it may be concluded that: (a) there exists a constant increase in time of the relative concentration of IASA in bone; only after one hundred hours following injection does the specific activity in bone exceed that in blood; (b) there is a constant increase in activity of the thyroid with time, which indicates that IASA is metabolized and deiodinated—and the iodide ions produced are trapped by the thyroid gland; and (c) there is an increase in time of the relative activity of practically all other tissues; this increase

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Table I

THE RELATIVE DISTRIBUTION OF 4-IODOALIZARIN 3-SULFONIC ACID IN CERTAIN TISSUES OF RATS*

Site	Time after Injection								
	¼ hr.	½ hr.	2 hr.	4 hr.	10 hr.	24 hr.	48 hr.	72 hr.	168 hr.
Blood	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Thyroid	0.32	0.46	0.54	0.93	1.37	3.65	10.7	22.3	130.00
Liver	1.15	0.83	0.94	0.76	0.68	0.82	1.43	1.7	
Spleen	0.89	1.17	1.03	0.73	0.64	0.84	1.63	2.1	
Lung	0.51	0.54	0.69	0.64	0.45	0.58	0.71	1.2	
Kidney	1.46	0.97	1.03	0.68	1.48	0.78	2.35	3.1	
Brain	0.013	0.018	0.022	0.025	0.038	0.045	0.13	0.18	
Muscle	0.14	0.14	0.16	0.18	0.22	0.31	0.30	0.29	0.86
Bone End	0.31	0.31	0.31	0.34	0.45	0.57	0.68	0.85	1.45

* Relative activity = $\frac{\text{Specific activity in tissue}}{\text{Specific activity in blood}}$.

indicates some retention of IASA in various organs.

The deiodination of IASA made necessary a comparison between the relative accumulation in bone and the relative concentration of iodide in the same organ. The relative accumulation of iodide in bone has been determined at the following doses of injected iodide: 500 μg., 25 μg., and carrier free I^{131}. The results are presented in Table II.

Table II

THE RELATIVE DISTRIBUTION OF IODIDE IN BONES OF RATS*

Time after Injection (hr.)	Iodide Dose		
	500 μg.	25 μg.	Tracer I^{131}
4	0.56	0.56	0.49
8	0.54	—	0.50
24	0.45	—	0.44

* Relative distribution in bone = $\frac{\text{Specific activity in bone}}{\text{Specific activity in blood}}$.

The relative distribution of IASA in certain bones is demonstrated in Table III. In this table the specific activities are given for the growing femur edges.

From Table III it may be seen that the accumulation of IASA in growing bone surpasses that in other bone areas. The fact that callus formation accumulates 7 times more IASA than the bone shafts in the same animal is worth noting.

The effect of IASA concentration on the distribution of IASA in various organs has

Table III

THE RELATIVE DISTRIBUTION OF 4-IODOALIZARIN 3-SULFONIC ACID IN BONES OF RATS

Site	Time after Injection							
	¼ hr.	½ hr.	2 hr.	4 hr.	10 hr.	24 hr.	48 hr.	72 hr.
Incisor	0.65	1.0	0.7	0.7	0.7	—	0.7	0.23
Skull	1.25	0.9	1.7	1.0	0.8	0.9	0.9	1.2
Vertebra	1.0	1.6	0.7	0.7	0.5	0.9	0.8	0.3
Shaft	1.3	0.9	1.1	1.1	0.8	0.73	0.52	0.33
Bone End	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Callus Formation	—	—	—	—	—	1.24	1.32	2.3

TABLE IV

THE EFFECT OF IASA CONCENTRATION ON ITS RELATIVE DISTRIBUTION*

	0.5 mg. IASA	5 mg. IASA	10 mg. IASA	0.25 mg. IASA + 2.5 mg. ASA
Blood	1.00	1.00	1.00	1.00
Spleen	0.33	2.75	1.90	1.60
Liver	0.80	0.45	0.74	0.45
Muscle	0.14	0.15	0.26	0.15
Brain	0.032	0.035	0.087	0.020
Bone End	0.31	0.55	0.53	0.49

* Relative concentration = $\frac{\text{tissue}}{\text{blood}}$ at eight hours after injection.

been investigated. Doses of 0.5, 5 and 10 mg. IASA have been administered and compared with a dose of 0.25 mg. plus 2.5 mg. of iodine free alizarin sulfonic acid (ASA). The results of this comparative study are given in Table IV.

From Table IV it may be concluded that the relative concentration of IASA in all organs, including bone, rises when we increase the dose of 0.5 mg. per rat tenfold. There is no further increase in the relative concentrations in bone when the dose is doubled from 5 to 10 mg. We may point out that there exists an increase in the relative concentration of IASA in bone in the presence of alizarin sulfonic acid. The relatively large accumulation of IASA in the spleen at high IASA and ASA doses should be noted.

The rate of excretion of IASA has been followed by calculating the biologic half life of the activity in various organs. The biologic half life was obtained by plotting the specific activity in a particular organ on a semilogarithmic plot versus time. The slope of the plot equals $0.693/\lambda$. In Table V the biologic half life of IASA is compared to that obtained for iodine 131 by Perlman *et al.*[6]

From Table V it is evident that the rate of excretion of IASA is determined by more than a single factor since the biologic half life changes with time. We may note that the excretion of IASA from bone is much slower than from other organs. This behavior may be compared with that of iodine in the thyroid gland. Another analogy with iodine metabolism is the fact that the rate of excretion increases with the dose of IASA, though the effect is not as spectacular as in the case of iodine.

DISCUSSION

The data demonstrate that 4-iodoalizarin 3-sulfonic acid, like alizarin sulfonic acid, accumulates in bone, especially in areas of new bone formation. The relative highest accumulation of the dye occurs in bone callus (Table III). Nevertheless the accumulation of the iodinated dye in bone is not markedly higher than the level in blood. It should be noted, however, that the data in Table I are given in units of relative specific activity per unit weight. If we calculate the relative specific activity per unit volume, we would find that bone tissue activity is three times greater than is shown by the data given in Table I, due to the higher

TABLE V

THE BIOLOGIC HALF LIFE OF IASA AND I^{131} IN RATS

	0.5 mg. IASA		5 mg. IASA	0.5 mg. I^{131}	Tracer I^{131}	
	Up to 48 hr.	48–170 hr.	Up to 48 hr.	Up to 48 hr.	Up to 48 hr.	48–200 hr.
Blood	13	32	10	5.2	67	215
Muscle	14	28	11.5	—	—	—
Thyroid	—	—	—	21	60	200
Bone	16	132	13	—	—	—

density of bone. After a relatively long period (for instance, one hundred and seventy hours for rats) we find a fivefold local activity in the growing part of bone as compared to blood, and twice as much in callus areas. If we compare the behavior of the dye with that of injected iodide (Table II) it is found that, whereas the iodide or its organic bound forms accumulate in bone to some extent (never above blood level), its relative specific activity does not increase with time. This means that there is little retention of inorganic or protein bound iodine in bone. There exists little effect of the iodide concentration in blood on the relative concentration of iodide in bone, in contrast to other tissues like thyroid where one finds limited capacity for iodide.[6] In the case of IASA, we do find a positive effect of the concentration of the dye in blood on the relative activity in bone (Table IV). When the level in blood is increased there is an increase in the relative concentration in bone, which is contrary to the case of iodide in the thyroid gland.

Probably there is a limited rate of clearance of the dye through the kidney or the feces. The excretion through the kidney and intestines is hardly dependent on the blood concentration of the dye, thus enabling the bone tissue to accumulate a higher concentration of the dye in a given time, before the level in blood falls below that in bone. An interesting fact in this respect is that alizarin sulfonic acid helps iodoalizarin sulfonic acid to accumulate in bone, most probably by slowing down its rate of excretion. The rate of excretion of the dye is slower than that of iodide at the same range of concentration, though it is faster than that of iodide at tracer level. There is evidence (Table I) that IASA undergoes metabolization and is deiodinated at a relatively slow rate (approximate biologic half life of seventy hours). Consequently, after one hundred and seventy hours there is no dye left in the organism except that which had accumulated in bone; all the remaining activity in the body at this time is due to iodide and to protein bound iodine formed from the metabolized dye.

From the rates of excretion and metabolization of the dye, it may be calculated that, at the time when the specific activity in bone rises significantly above the activity of the blood, only 1 part in 300 of the injected dye is retained in the organism. This is mainly concentrated in the growing parts of the bone. Measuring a certain growing area of bone, or a malignant bone tissue, we may find only a small percentage of the amount of the retained dye. The amount of dye we may expect under these circumstances in a particular volume of bone may be, even under favorable conditions, below 1 part in 10,000 of the injected dose. Considering the application of the labeled dye as a tracer for growth areas in bone, this would mean a quite impractical initial dose of radioactive dye, even if we were to block the thyroid gland in order to avoid accumulation of iodide by the gland. The same reasoning would apply if 4-iodoalizarin were used as a contrast medium in roentgenography. In order to accumulate only 50 mg. of the dye in a certain volume it would be necessary for the patient to ingest 0.5 kg. of IASA.

We may conclude, therefore, that, although I^{131} alizarin sulfonic acid accumulates especially in areas of physiologic and pathologic new bone tissue formation, its efficiency of concentration, its rate of excretion, and the fact that it is metabolized make its application as a tracer impractical for clinical use. It is suggested that other chelating agents may have a higher affinity for bone, a lower rate of excretion and a higher stability, thus enabling them to be used as tracers or as contrast media for the study of bone.

SUMMARY

1. The distribution of 4-iodoalizarin 3-sulfonic acid in various organs has been determined, using I^{131} labeled dye. The organs examined included liver, spleen, thyroid, kidneys, blood, brain, lungs and muscle, with special reference to bone tissues.

2. It has been found that the labeled dye accumulates in bone, and especially in growing bone formations. The specific activity in bone exceeds that in blood only after most of the dye has been excreted. A comparative examination has been performed determining the accumulation in bone formation of I^{131} injected as an inorganic iodide.

3. It has been found that iodoalizarin undergoes metabolization and is deiodinated. The rate of excretion of iodoalizarin has been determined and compared to the rate of excretion of iodine injected as an inorganic iodide.

4. Considering the rate of accumulation, metabolization and excretion of 4-iodoalizarin 3-sulfonic acid, its application as a tracer for the study of physiologic or pathologic new bone formations was evaluated. It may be concluded that the application of the labeled dye as a tracer is impractical.

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THE EFFECTS OF ROENTGEN IRRADIATION ON ADRENAL CORTICAL FUNCTION IN MAN*

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IN 1954, a preliminary study by Soanes and Dodson[18] of a group of patients with testicular tumors suggested that some alteration of adrenal cortical function followed the administration of therapeutic doses of roentgen rays to the abdomen. The results of these studies, though inconclusive, raised the interesting question of whether transient or permanent adrenal cortical alteration occurred following such therapy to the region of the adrenal glands. Previous workers[2,4,21,23] have shown that with very large doses of roentgen rays there are morphologic changes demonstrable in the adrenal cortex. Aside, however, from the depletion of the sudanophilic substance[21] the dosage used to produce such changes has been far above that used for diagnostic or therapeutic purposes in humans. Alterations in adrenal function, resembling adrenal cortical insufficiency, have also been reported by a number of investigators,[7,17,23] but case histories of most of these patients again raise a question as to possible extrinsic complicating factors and the effect of the very high doses of radiation used. Desjardins,[2] after reviewing the experimental aspects of the subject, concluded in 1928 that, in spite of the morphologic disturbances in the adrenal cortex which may be produced by roentgen irradiation, the health of the animals did not appear to be deleteriously influenced. He, therefore, assumed that the adrenal gland was relatively resistant to radiation as compared with other organs of the body. Desjardins and Marquis[3] showed that 55 patients with apparently normal adrenal glands failed to reveal manifestations of adrenal insufficiency following therapeutic doses of roentgen radiation. Most of their work, however, was directed primarily at measuring what is now known to be medullary rather than cortical function, and the methods of study of true cortical function were very crude.

Lawrence,[8] using minimal lethal doses of total body roentgen irradiation on dogs, showed that there was a significant increase in steroid excretion several days following irradiation, and that the values then fell to normal or subnormal levels with a gradual return to normal. Rosenfeld *et al.*[16,22] noted a decreased secretion of hydrocortisone, cortisone, and other steroids by isolated calf adrenals which were perfused with ACTH-containing blood and exposed to Co^{60} irradiation. Patt *et al.*[10] observed a marked increase in adrenal weight and a decrease in adrenal cholesterol content following whole body roentgen irradiation of rats at levels of 650 r (LD_{50}) and 900 r (LD_{100}). After a whole body dose of 200 r (sublethal), however, there was little change. Leblond and Segal[9] have reported that adrenal hypertrophy occurs as a secondary response to roentgen irradiation of other portions of the body, but several early observers[2,6,13] found no such effect after direct irradiation of the adrenals. It should be noted that most of the early investigations pertained to humans and were rather poorly documented with animal experimentation, utilizing excessively large dosages, and generally whole body irradiation. The problem encountered in the human subject undergoing roentgen

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therapy is one of large but localized doses of radiation, which may or may not directly strike the adrenal glands.

It was, therefore, decided to study the adrenal function of a group of patients with testicular tumors to whom therapeutic doses of roentgen rays were administered through abdominal portals which included the region of both adrenal glands. This paper presents the findings of this study and discusses their significance.

MATERIAL

The 9 patients selected for this study ranged in age from twenty to forty-one years and all were Caucasian. They are listed in Table 1, together with their diagnoses and the results of a six to seven year

TABLE I

DIAGNOSIS, TREATMENT AND FOLLOW-UP OF PATIENTS

Case	Age at Surgery	Surgery	Pathologic Diagnosis	Follow-up
1	22	Right orchiectomy	Seminoma	Living and well, 75 mo.
		Right inguinal lymph node biopsy	No significant pathologic changes	
2	26	Right orchiectomy	Seminoma with vascular invasion and interstitial cell hyperplasia	Living and well, 73 mo.
3	41	Right orchiectomy	Seminoma	Living and well, 72 mo.
4	39	Left orchiectomy	Seminoma with invasion of spermatic vein	Living and well, 68 mo.
		Excision of breast tissue, bilateral	Gynecomastia	
5	22	Right orchiectomy	Embryonal carcinoma	Living and well, 66 mo.
6	20	Right orchiectomy	Teratoma with embryonal carcinoma	Histologically benign teratoma, left supraclavicular region 5 mo. later—no other tumors; living and well, 71 mo.
		Right retroperitoneal lymph node dissection	No significant pathologic change	
7	40	Right orchiectomy	Embryonal carcinoma	Died of pneumonia, no tumor recurrence in 80 mo.
		Right radical retroperitoneal lymph node resection	Reactive hyperplasia	
8	21	Left orchiectomy	Teratoma with embryonal carcinoma	Died with generalized metastases in 7 mo.
		Retroperitoneal lymph node dissection	Retroperitoneal metastases	
9	20	Left orchiectomy	Teratoma with embryonal carcinoma and choriocarcinoma	Living and well, 66 mo.

clinical follow-up. All had testicular tumors which were surgically removed. At the time of surgery none of the patients showed evidence of renal or adrenal metastases, and only one showed evidence of low retroperitoneal metastases. Two, however, had vascular invasion in the spermatic cord. The pathologic specimens of these patients were examined independently by 4 pathologists and the diagnoses were reviewed and concurred in by the Armed Forces Institute of Pathology.

The purpose of the study was thoroughly explained to all patients and it was felt that they understood the necessity of complete cooperation, and all volunteered to participate. Insofar as possible, checks were maintained by nursing and medical personnel on the collection of the urine specimens. In almost all cases the 24-hour urine volumes were reasonable, and 24-hour creatinine excretion studies confirmed that complete 24-hour urine specimens were obtained.

METHOD

Surgical orchiectomy was performed by the usual procedure, and in the cases indicated (Table 1) retroperitoneal lymph node dissection was also done. Postoperatively the adrenal glands were anatomically defined, using the upper poles of the kidney shadows on a flat roentgenogram of the abdomen as a guide for their location. It was felt that in all of the patients the adrenal glands were located with certainty. The perimeters of each patient's prescribed portals for radiation therapy were then outlined on the skin with lead markers and a flat roentgenogram of the abdomen was taken to ensure that the renal shadows were within the confines of the portals, and thus that the adrenal glands were within the field of direct irradiation. Treatment was then administered with the specific factors, dosage schedules, and relatively large portals indicated in Table II and Figures 1 through 4. It should be noted that in Case 7 the adrenal glands probably did not lie entirely within the direct projections of either the abdominal or epigastric portals. The right adrenal gland was almost completely within the epigastric portals and the left partially so. Both were immediately adjacent to the superior edge of the abdominal portals. In Case 9 a 15×7 cm. lead plate was placed over the epigastrium on the days indicated (Fig. 4) to protect the adrenal glands from direct irradiation.

Twenty-four hour urine specimens were collected in chemically clean bottles containing a few crystals of thymol as a preservative. The specimens were refrigerated throughout the period of collection, and then transferred to a deep freeze at a temperature of approximately −5° C. and kept for analysis. The 17-ketosteroid excretion was determined by the method of Robbie and Gibson,[15] and the 17-hydroxycorticosteroids were determined by the Porter-Silber[11] method as modified by Reddy *et al.*[12] Adrenal cortical function was evaluated by the method described by Renold *et al.*[14] except that 40 international units of adrenocorticotrophic hormone (ACTH) were administered by continuous intravenous drip over a ten hour period. In a few instances the two day ACTH test of Thorn *et al.*[20] was used to obtain the additive effect of 40 international units of ACTH similarly administered on two consecutive days.

Almost daily 24-hour urine collections were made from the beginning of the control period throughout the course of irradiation and for a short period following cessation of irradiation. Intermittent follow-up studies were performed during the ensuing ninety days, as the patients were available. ACTH stimulation studies were performed on the days indicated in the respective figures. All collected urine specimens were analyzed for the 24-hour excretion of 17-ketosteroids, and selected specimens were analyzed for 17-hydroxycorticosteroids in Cases 3 through 9, since the 17-hydroxycorticosteroid analyses did not become available until the 40th day of the study of Case 3. In each case the patient acted as his own steroid excretion control (except 17-hydroxycorticosteroid excretion in Case 3).

TABLE II

ROENTGEN THERAPY OF PATIENTS

Case	Portals and Size (cm.)*	Duration (days)	Distance Skin to Depth (cm.)	Per Cent Depth Dose	Tissue Dose (r)*		Total Adrenal Dose (r)
					Daily	Total	
1	Opposing posteroanterior and anteroposterior abdomen 15×30	31	9.5	72	54/108	2,592	2,592
2	Opposing posteroanterior and anteroposterior abdomen 15×30	35	9.0	75	74/112	2,607	2,607
3	Opposing posteroanterior and anteroposterior abdomen 15×30	29	9.0	75	56/150	2,512	2,512
4	Opposing posteroanterior and anteroposterior abdomen 15×30	28	9.0	75	75/150	2,569	1,569
5	Opposing posteroanterior and anteroposterior abdomen 15×30	35	9.5	72	72/144	3,420	3,420
6	Opposing posteroanterior and anteroposterior abdomen 15×30	37	7.5	86	65/129	3,526	3,526
7	Opposing posteroanterior and anteroposterior abdomen 20×20	39	10.0	64	64/128	3,392	0†
	Opposing posteroanterior and anteroposterior epigastrium 12×12	35	10.5	48	72/120	3,216	3,216†
	Right lateral abdomen 10×10	1	15.0	27	81	81	0
8	Opposing posteroanterior and anteroposterior abdomen 18×30	36	8.5	78	59/156	3,510	3,510
	Opposing posteroanterior and anteroposterior mediastinum 10×20	30	8.5	66	66/132	2,904	0
9	Opposing posteroanterior and anteroposterior abdomen 15×7 (when not shielded)	37	10.5	64	32/128	2,112	2,112
	Opposing posteroanterior and anteroposterior abdomen 15×30 (with 15×7 shield part of time)	37	10.5	64	32/128	3,484	0

Note: In all cases a Maximar roentgen-ray machine was used with the following physical factors: 220 kv.; 0.5 mm. Cu, 1 mm. Al filter; 1.35 mm. Cu half value layer; 15 ma.; 70 cm. target source distance; 21.6 r/min. (air). In general, paired anteroposterior and posteroanterior corresponding treatment fields were irradiated on alternate days with no therapy on Sundays and holidays. Data on day to day treatment are detailed in Figures 1 through 4.

* For detailed locations of portals and record of daily treatments see Figures 1 through 4.

† In Case 7 the adrenal glands were not completely within the epigastric portals, and were very close to the abdominal portals.

In all cases, except Case 2, ACTH stimulation studies were done at or before the institution of radiation therapy; so again each patient acted as his own internal control.

RESULTS

The results of the steroid analyses on the 9 patients are summarized in Figures 1 through 4. These show the detailed day by day record of the 17-ketosteroid and 17-hydroxycorticosteroid excretion, and of the daily dose of radiation. For each patient or group of patients a sketch showing the detailed anatomic location of the portals used for irradiation is included. All steroid

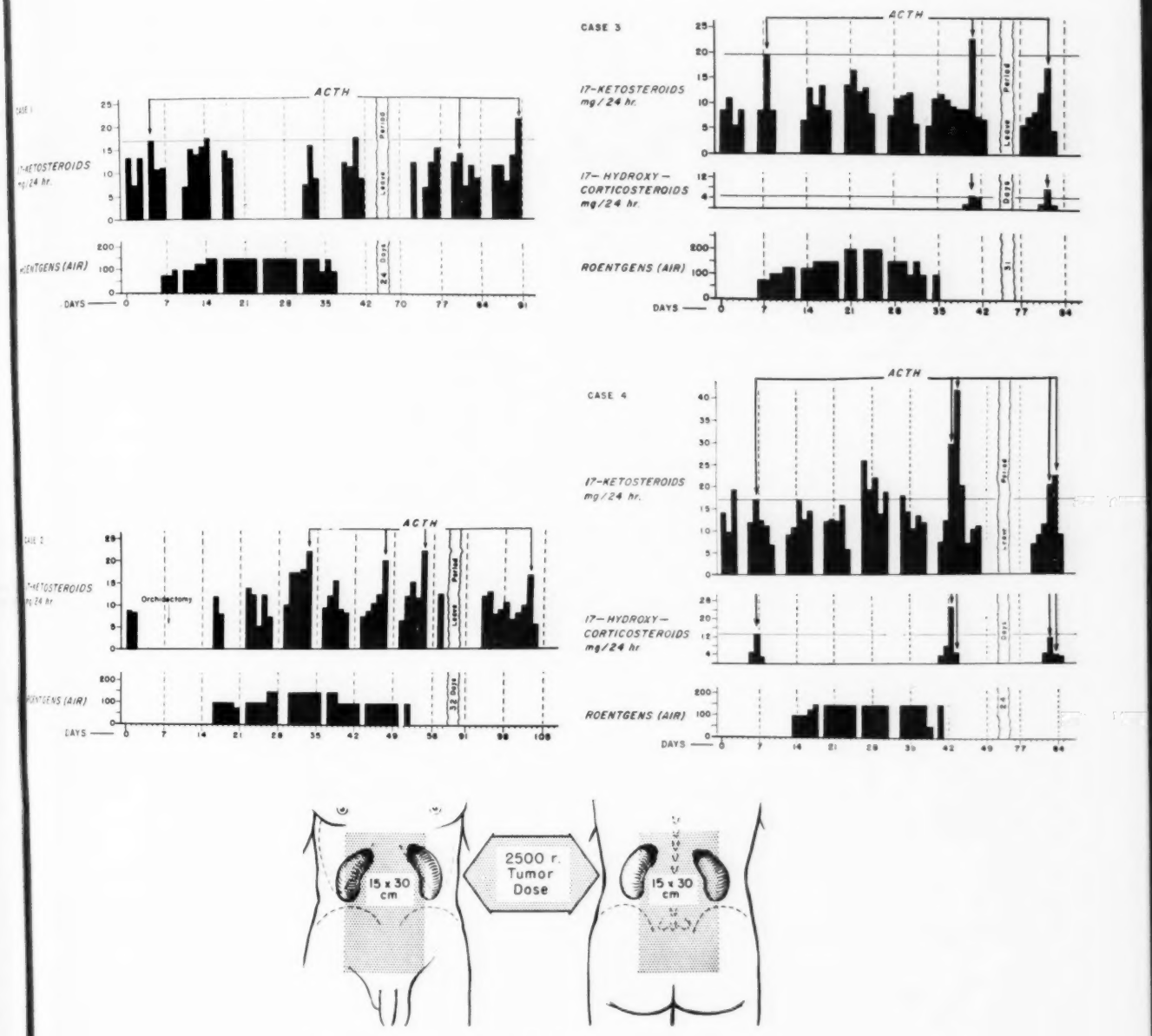
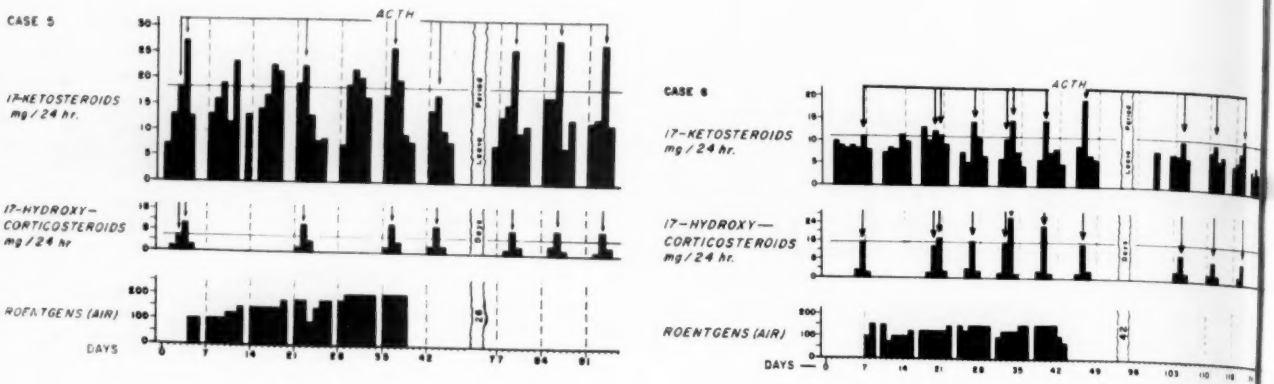


FIG. 1. Summary of irradiation portals and data of roentgen therapy and steroid excretion in Cases 1 through 4.

values are expressed in milligrams excreted in the urine for twenty-four hours. Days on which 40 international units of ACTH were administered intravenously to determine the effect of adrenal stimulation are indicated by arrows. The horizontal lines on the portions of the charts showing the steroid excretion indicate the level of steroid excretion on the first day of ACTH stimulation, prior to the commencement of irradiation. In some cases ACTH stimulation was done on two consecutive days but the steroid excretion level on the first day of stimulation was selected as the base line. Thorn *et al.*[20] have previously reported an additive effect of ACTH when administered on consecu-



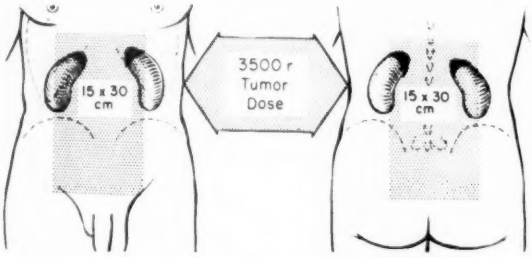
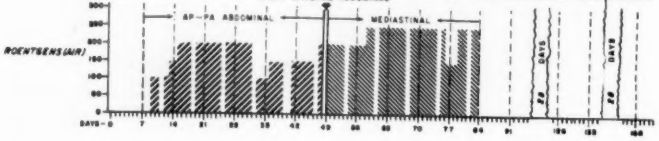


FIG. 2. Summary of irradiation portals and data of roentgen therapy and steroid excretion in Cases 5 and 6.



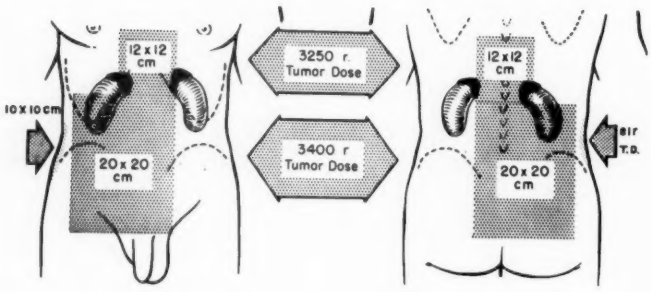


FIG. 3. Summary of irradiation portals and data of roentgen therapy and steroid excretion in Case 7.

tive days; therefore, it was felt that a more satisfactory and uniform base line stimulation level would be obtained by using the excretion level on the first day of stimulation.

Pre-irradiation 17 ketosteroid studies were carried out on each patient for several days. Examination of these values for each patient showed a marked day to day variation of the 24-hour urinary 17-ketosteroid excretion, with variations up to 100 per cent of the lowest value obtained. Such variations persisted throughout the period of observation, largely masking any actual change in adrenal cortical activity due to the irradiation. In most of the cases an intravenous ACTH stimulation study was done on or just prior to the first day of irradiation and repeated later in the course of therapy. Both 17-ketosteroid and 17-hydroxycorticosteroid analyses were carried out the day before, on the day or days of ACTH stimulation, and the day following. In the majority of patients the 17-ketosteroid excretion on the first day of ACTH stimulation was between 50 and 100 per cent higher than the highest nonstimulated value, but in Case 4 one of the control nonstimulation days gave a value that was higher than that on the first day of ACTH stimulation. In Cases 6 and 8 only a slight rise above the highest base line value was observed. The increase in 17-hydroxycorticosteroid excretion, however, was found to be much more pronounced, varying from a 100 to approximately a 400 per cent increase. From Figures 1 through 4 it is apparent that some trends in the 17-ketosteroid excretion values exist; however, the 17-hydroxycorticosteroid excretion determinations reveal these in a much more clear-cut manner. The marked day to day variations of the 17-ketosteroid excretion makes any interpretation of such data hazardous.

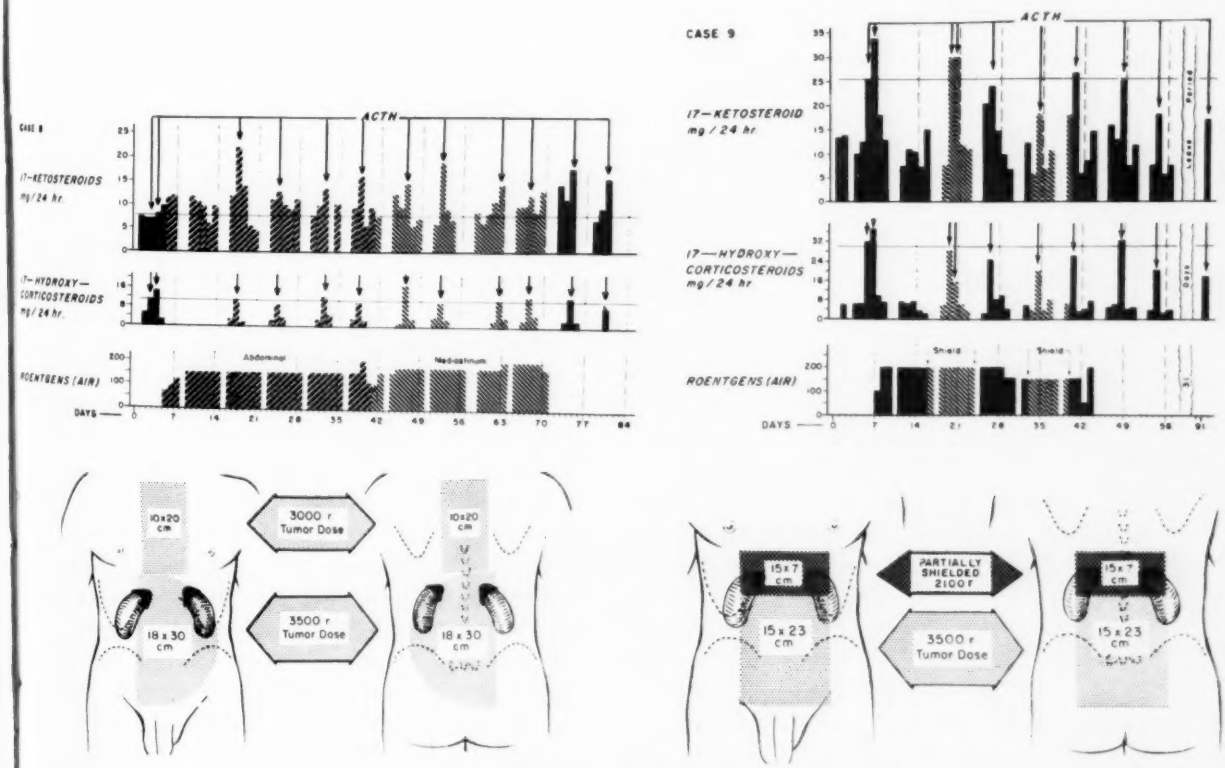


Fig. 4. Summary of irradiation portals and data of roentgen therapy and steroid excretion in Cases 8 and 9.

Where there are some differences in the excretory patterns of the two steroids, as in Cases 6, 7 and 8, it would appear that the 17-hydroxycorticosteroid data are those on which interpretations of adrenal cortical activity should be based.

The data in Figures 1 through 4 show a mild to moderate increase in 17-hydroxycorticoid excretion in response to intravenous ACTH stimulation during the latter part of radiation therapy and immediately following it, with a subsequent return to normal or below normal excretion levels. The increases range from an apparently insignificant amount in Cases 7, 8 and 9 to almost a 100 per cent increase in Cases 4 and 5. In some cases (especially in Cases 6, 7 and 9) a decrease in 17-hydroxycorticoid excretion in response to intravenous ACTH stimulation was observed late in or following the termination of radiation therapy. The two day ACTH stimulation tests revealed the expected increase in 17-hydroxycorticoid excretion on the second day of stimulation compared with the first, except in Cases 4 and 9 where after more than 2,000 r tissue dose of radiation to the adrenal glands the second day excretion value dropped off instead of rising. In Case 6 after 1,200 r, and again after 2,500 r, the second day excretion value was higher than that of the first day, as in the control tests.

Case 8 is the only patient in this series on whom autopsy material could be obtained. The autopsy revealed widely disseminated metastases of embryonal carcinoma of the testis with almost complete replacement of the left adrenal gland. The right adrenal gland, however, was not involved by tumor and careful study showed no significant histologic change. The patient was markedly cachectic at the time of death and Sudan IV stains of sections of the adrenal gland revealed a mild to moderate reduction of sudanophilic substance in the adrenal cortex, but the changes were consistent with the degree of cachexia and chronic illness of this patient. Hematoxylin and eosin, Masson trichrome, and reticulum stains revealed no evidence of any significant change in architecture and no increase in fibrous or reticular elements. The relative thicknesses of the zona glomerulosa, the zona fasciculata, and the zona reticularis were essentially normal. No evidence of significant vascular changes was found. Examination of sections of adrenal glands from other patients receiving large amounts of radiation to abdominal portals revealed no specific changes ascribable to the irradiation.

DISCUSSION

The steroid data clearly reveal the inadequacy of 17-ketosteroid excretion and the relative reliability of 17-hydroxycorticosteroid excretion in measuring adrenal cortical function. The effects of specific adrenal cortical stimulation are largely masked in many cases by the presence of considerable extra-adrenal 17-ketosteroid which is being simultaneously excreted. The 17-hydroxycorticosteroids are much closer metabolically to the adrenal cortex than the 17-ketosteroids, which may come from many different sources. The reasons for the excess extra-adrenal steroid are not apparent since all the patients are young men who have one testis and similar disease processes. It is interesting to note that in Case 9, which demonstrates very high unstimulated 17-ketosteroid excretion values, there is still a marked ACTH stimulation effect. This shows that the ACTH stimulation test is a measure of adrenal cortical reserve capacity.

Various previous workers[1,5,17,19] have shown that 17-ketosteroid excretion values rise for a short period during stress and then fall back to base line levels. These studies have been made largely in conjunction with trauma and disease, and such studies have not been reported in cases receiving roentgen irradiation. Selye[17] has proposed his theory of the "general adaptation syndrome" and the accompanying adrenal response to stress, which is consistent with the above observations. From the cases studied in this series, it is felt that prolonged irradiation represents severe stress, and in consonance with Selye's theory there

is an increased response of the adrenal cortex to intravenous ACTH stimulation. In most cases the steroid excretion values returned to approximately control levels in the period following cessation of irradiation. In some cases, however, an apparent permanent decrease in the capability of the adrenal gland to respond to intravenous ACTH stimulation after the delivery of larger therapeutic doses of radiation was noted. Since the adrenal glands of the one patient in this series who came to autopsy, as well as those of patients receiving similar high doses of roentgen radiation, showed no significant morphologic change, it is difficult to identify the exact pathologic process.

The most marked adrenal cortical impairment occurred in Cases 6 and 7, who received approximately 3,500 r tissue dose through portals encompassing the adrenal glands. Case 7 also received an additional 3,400 r tissue dose through other abdominal portals which did not include the adrenal glands. Although in this patient the adrenal glands were not completely within the field of either pair of anterior and posterior portals, they were largely included in the epigastric portals and very close to the superior margin of the abdominal portals, thus undoubtedly receiving a high dose of radiation. Adrenal cortical impairment occcurred without prior evidence of any significant enhancement of the adrenal cortical response to intravenous ACTH stimulation. It should be noted that relatively few 17-hydroxycorticosteroid analyses were made on this patient, and it is possible that some enhancement occurred but was missed. In Case 8 two separate pairs of portals (one abdominal pair including the adrenal glands and one mediastinal pair) were used, giving 3,500 r tissue dose to the adrenal glands. This patient showed a slight increase in adrenal cortical response to intravenous ACTH stimulation which persisted throughout therapy, but he was lost to steroid follow-up two weeks later. In Cases 1 through 6 only one pair of abdominal portals, which included the adrenal glands, was irradiated. Of these, Cases 4, 5 and 6 showed marked enhancement of adrenal cortical response to intravenous ACTH stimulation. Cases 5 and 6 received approximately 3,500 r tissue dose to the adrenal glands as compared to approximately 2,500 r in Cases 1 through 4. Case 6, however, was the only one of these patients to demonstrate subsequent adrenal cortical impairment.

The two day intravenous ACTH stimulation tests, performed prior to the beginning of irradiation, revealed a cumulative response to intravenous ACTH stimulation, as previously reported by Thorn *et al.*[20] Those performed late in the course of therapy, or following it, revealed an interesting pattern. In Case 4 after 2,500 r tissue dose to the adrenal glands, the 17-hydroxycorticosteroid excretion was markedly less on the second consecutive day of intravenous ACTH stimulation, and a similar effect was noted in Case 9 after approximately 2,000 r tissue dose of radiation to the adrenal glands. In Case 6 similar tests following tissue doses of approximately 1,200 r and 2,500 r did not show such a reversal. These data suggest that there may have been impairment of adrenal cortical reserve not manifested by the one day intravenous ACTH stimulation test. Thus, smaller doses of radiation (of the order of 2,000 r) than the 3,000–3,500 r necessary to manifest adrenal cortical damage by the one day intravenous ACTH test may reduce the ability of the organism to withstand stress situations. Further studies of this type with various adrenal and ACTH blocking substances would appear warranted to assess such lesser degrees of damage.

In an attempt to determine whether the alterations in adrenal cortical response were due to the direct effects of irradiation or to generalized toxic effects, regardless of whether the irradiation portals directly involved the adrenal glands or not, an attempt was made in Case 9 to alternately shield and irradiate the adrenals. Unfortunately, no significant enhancement effect

was encountered in this patient. During the second period of shielding, however, a drop in steroidogenesis in response to intravenous ACTH stimulation was noted, with a return to base line levels on redirect irradiation, followed by another drop after irradiation was completed. This is suggestive of an enhancement effect during direct irradiation of the adrenal glands rather than a systemic effect. It also suggests that the damage is the result of direct irradiation, becoming evident after cessation of the stimulatory effect during actual active irradiation, provided the dose has been large enough.

Cases 7 and 8 should cast some light on the problem of whether direct adrenal gland irradiation or generalized toxic effects are of more significance, since these patients received radiation therapy to portals including the adrenal glands and also to other portals. In Case 8 a 17-ketosteroid stimulation effect in response to intravenous ACTH was noted early during irradiation of portals including the adrenal glands, but only a transient true adrenal cortical stimulation as shown by the excretion of 17-hydroxycorticosteroids occurred. This was at the end and very shortly following the direct adrenal gland irradiation, occurring early in the irradiation of the mediastinal portals. In Case 7 little stimulation was noted, but insufficient analyses were performed. Definite adrenal cortical depression occurred late and persisted. Early stimulation and late depression were observed in Case 6 where only adrenal gland portals were irradiated.

It is felt that to obtain more significant data on this matter it would be necessary to study an additional series of patients receiving similar therapeutic doses of radiation to another area, for instance the chest, and then to compare them with Cases 1 through 6 in this series. The data obtained in this series, however, would appear to clearly indicate that enhancement does occur when the adrenal glands are directly irradiated. The data also suggest that the adrenal gland damage manifested by depressed steroidogenesis in response to intravenous ACTH stimulation is the result of such direct irradiation, generally following large doses.

The degree of response of the adrenal cortex to intravenous ACTH stimulation seems to be dependent on the tissue dose of radiation administered to the adrenal glands. Marked individual variation is apparent from this study. Tissue doses to the adrenal glands of approximately 2,500 r generally produce increased adrenal cortical activity in response to intravenous ACTH stimulation followed by a return to base line values with no subsequent impairment (Cases 1 through 4). Tissue doses of 3,500 r to the adrenal glands usually produce an initital stimulation followed by subsequent impairment as manifested by the *one* day intravenous ACTH stimulation test (Cases 5 through 8), while tissue doses of 2,000 to 3,000 r produce an initial stimulation with simultaneous impairment of the response to the *two* day intravenous ACTH stimulation test (Cases 4, 6 and 9).

SUMMARY

Nine cases of patients with testicular tumors receiving therapeutic doses of roentgen rays to the region of the adrenal glands are presented. The 17-ketosteroid and 17-hydroxycorticosteroid excretion studies were carried out prior to the initiation of radiation therapy, during therapy, and for a follow-up period. Adrenal steroidogenesis was evaluated by the response of the adrenal to stimulation with 40 units of ACTH administered intravenously over a ten hour period on one day, or on two successive days.

The data indicate a variable degree of enhancement of adrenal cortical steroidogenesis during or immediately following radiation therapy to the adrenal glands in the majority of patients, presumably reflecting the "general adaptation syndrome" to stress.[17] Most patients acquired a mild degree of adrenal cortical impairment secondary to such irradiation. The data indicate that the administration of more than

2,000 r tissue dose to the adrenal glands produces increased adrenal cortical steroidogenesis during irradiation in response to the *one* day intravenous ACTH stimulation test. Less than 2,000 r tissue dose produces no impairment or stimulation of adrenal steroidogenesis or reserve as measured by *one* or *two* day intravenous ACTH stimulation. Administration of 2,000–3,000 r tissue dose produces a transient stimulation with a simultaneous loss of adrenal cortical reserve as shown by intravenous ACTH administration on *two* consecutive days. More than 3,000 r tissue dose results in transient stimulation followed by subsequent adrenocortical impairment as manifested by stimulation by *one* day of intravenous ACTH administration. Following 3,500 r tumor dose, the adrenal glands still appear to have a normal amount of steroidogenesis under nonstress conditions, but their ability to respond to stress is markedly limited.

The data on patients receiving roentgen radiation through portals including the adrenal glands and through other portals suggest that the enhancement and impairment observed are both due to direct irradiation of the adrenal glands, but generalized secondary systemic toxicity may play a role. One patient who died showed no evidence of functional adrenal cortical impairment after 3,500 r tumor dose to the adrenal glands and 3,000 r tumor dose to the mediastinum. At autopsy, no histologic changes of the adrenal cortex were found. Study of the adrenal glands of other patients receiving similar doses of therapeutic roentgen radiation to the adrenal glands likewise failed to reveal any characteristic or significant histologic changes.

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SENSITIZATION AND RECOVERY PHENOMENA AFTER EMBRYONIC IRRADIATION*

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DURING the course of studies on the effects of radioactive phosphorus on the development of the rat embryo,[8,9] we found a much greater incidence of malformations when injection was made after six or after eight days of gestation than was expected on the basis of previous studies by Wilson *et al.*[10,11,12] They had noted that acute external roentgen irradiation of the rat embryo did not produce malformation when administered at eight days of gestation or before. Their experiments, among others, showed that a wide array of malformations, which were largely characteristic of the age at the time of irradiation, could be produced by irradiation at nine days of gestation and therefter. Russell's[7] studies likewise demonstrated that irradiation during the comparable stages of development of the mouse did not induce anomalous development in this species. It was our first inclination to explain our findings on the basis of P^{32} remaining at nine days of gestation and thereafter. This was not possible, however, since we had found that too little radiophosphorus remained in this period to explain the incidence of malformation that was found.[9]

In searching for other possible explanations for this phenomenon, our attention was attracted to the recent revival of interest in the processes of recovery from radiation. In the use of fractionated radiations to determine the rate of recovery, two exposures are usually administered, an initial exposure followed by a second test dose. The first exposure is usually arbitrarily given as one half of the previously determined median lethal dose or LD_{50}. Implicit in this usage is the consideration that this initial increment of radiation would be without a grossly detectable effect, although it would of necessity have some effect which could be experimentally determined. This initial exposure may essentially be regarded as a sensitizing dose of radiation.

As early as 1920, a theory of recovery had been proposed by Kingery[4] according to which radiation produces some hypothetical decomposition product which in turn elicits clinical manifestations when present in sufficient concentration. He further postulated that recovery consisted of an exponential loss of this material. Although current concepts of radiation recovery do not require the presence of such a substance, an exponential recovery is commonly accepted. The so-called "Pfahler-Kingery" or "saturation" method of radiation therapy, which was proposed by Kingery[4] and expanded by Pfahler,[5,6] was based upon experimental and empirical estimates of these recovery times. This method consisted of fractionation with doses of decreasing size to establish and then maintain a plateau of effect. Recently, Du Sault[2] has proposed that a more careful study be made of fractionation effects to enable treatment planning to be derived more effectively, making use of the differential recovery rates which may be shown to occur between normal and neoplastic tissues in some cases.

These considerations have led us to experimentally examine the possibility that irradiation earlier in gestation might sensitize the embryo so that small amounts of radiation from P^{32} residual at nine or ten days of gestation would produce an effect greater than might otherwise be expected.

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MATERIAL AND METHODS

Virgin female rats of the Holtzman strain, weighing between 180 and 200 gm., were used in these experiments. These animals were caged nightly with males of the same strain and vaginal smears taken daily thereafter. Nine o'clock in the morning of the day on which the smear was found to contain sperm was considered to be the time of fertilization.

Groups of 10 to 12 pregnant animals were exposed to one of several doses of roentgen rays after six or after nine days of gestation. The animals were individually enclosed within segments of a lucite wheel-shaped device which rotated about the axis of the roentgen-ray beam. Exposure was made at 250 kv. peak with a G. E. Maximar machine. Operating this unit at 15 ma. with a parabolic aluminum field-flattening filter in addition to a 0.5 mm. copper and 1 mm. aluminum flat filter gave a beam of 1.75 mm. copper half value layer and a dose rate of approximately 16 r per minute.

From the examination of the resultant dose-response curves, which are shown in Figure 2, it was seen that treatment with doses of 110 r or less after six days of gestation did not increase post-implantation mortality above control levels. Neither this dose, nor even higher doses, produced any malformations when administered at this time of gestation. Accordingly, pregnant females were subjected to a sensitizing dose of 110 r at six days of gestation. They were again exposed three days later, at nine days of geststion, to a variety of roentgen-ray doses to establish the new dose-response curve.

In all cases, the female rats were sacrificed after fourteen days of gestation and the fetuses removed, weighed, and examined for gross malformations. The mortality percentage and weight depression at fourteen days of gestation were plotted against dose on probability graph paper and the ED_{50} determined by the method of Litchfield and Wilcoxon.[3] Similar functions were calculated for anomalous development in terms of the radiation dose which would produce a 50 per cent incidence of various specific gross abnormalities. For the purposes of this study, this was analyzed as the percentage of animals showing an arbitrary amount of decrease in the relative length of the mandible, reduction of the size of the external aspect of the eye, or failure of the processes composing the maxilla to close. The minimum extent of change that was denoted abnormal for the purposes of these calculations is demonstrated in Figure 1, *B* and *D*.

RESULTS

The 3 dose-mortality curves, in terms of the percentage of the embryos killed by fourteen days of gestation, are shown in Figure 2. It may be seen that these curves are essentially parallel to each other; this is confirmed by statistical analysis. Using the method of Litchfield and Wilcoxon,[3] an ED_{50} value of 178 r may be obtained for treatment at six days and 147 r at nine days of gestation; these differ significantly at the 95 per cent confidence level. When the pregnant females were given a preliminary exposure of 110 r at six days, only 115 r additional at nine days of gestation produced 50 per cent mortality by fourteen days. This displacement of the response curve by 32 r to the left implies that about 29 per cent of the six day exposure remains effective three days later for enhancement of the lethal effect.

Although all 3 curves have essentially the same general shape, there is a difference notable in terms of the apparent threshold, *i.e.*, the dose below which no effect is noted. It is seen that there is a distinct threshold of about 110 r or 80 r when irradiation was performed at either six or nine days of gestation, respectively. This threshold was not found when the exposure at nine days was preceded by a sensitizing exposure of 110 r at six days.

The corresponding curves for weight depression after irradiation at six or at nine days of gestation, which are not presented, show threshold values similar to those seen for mortality. The shapes are distinctly

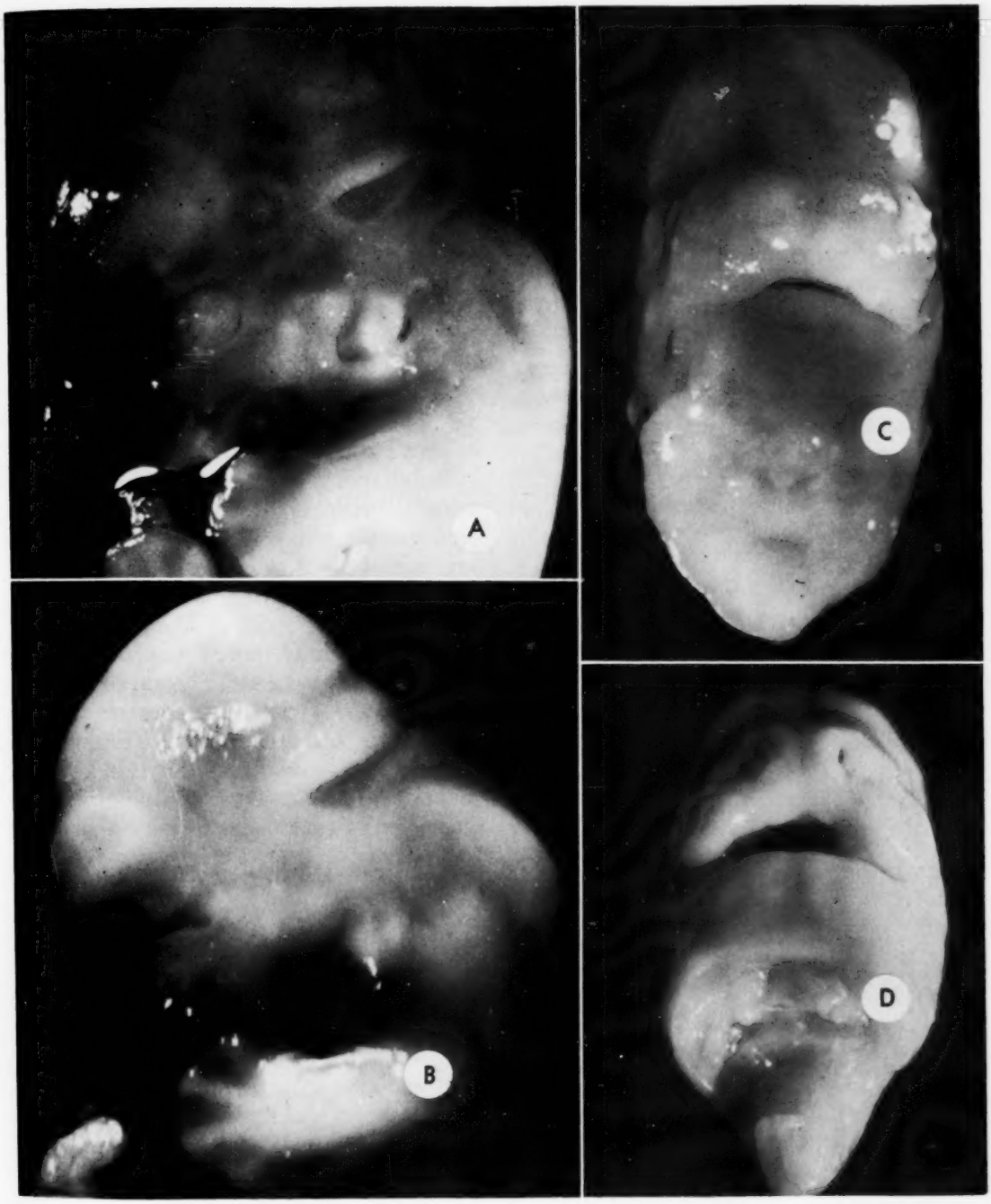

Fig. 1. Gross anomalies used as criteria. (*A*) Profile of normal fourteen day rat embryo. (*B*) Profile of irradiated fourteen day rat embryo. Note decreased size of eye and nonclosure of maxillary processes. (*C*) Ventral aspect of head of normal fourteen day rat embryo. (*D*) Ventral aspect of head of irradiated fourteen day rat embryo showing shortened mandible.

different, however, in that they both plateau and are essentially horizontal over the upper dose range. The curve obtained with pretreatment at six days does not show such a threshold. Additionally, it has a lesser slope than the other 2 curves although it approaches the same maximum value of weight depression.

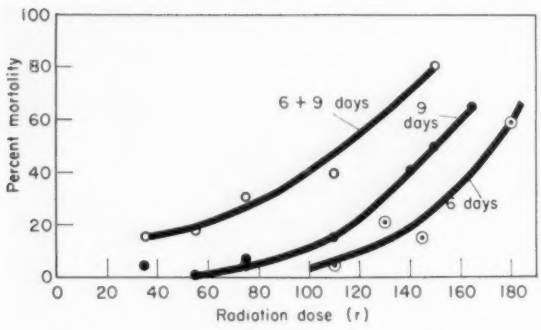

FIG. 2. Percentage mortality at fourteen days of gestation of embryonic rats after irradiation with various doses at six or nine days or pretreated at six days and again exposed at nine days of gestation.

As was indicated above, a reduction in the relative size of the mandible equal to or greater than that shown in Figure 1*D* has been considered anomalous. The percentage of fourteen day fetuses showing this amount of mandibular shortening has been plotted against dose in Figure 3.

At the levels of radiation used in this experiment, a 50 per cent incidence of mandibular shortening was not attained. The probit lines were extended and the ED_{50} values estimated; these were 180 r and 132 r for irradiation at nine days and for six plus nine days respectively. Because of this extrapolation as well as because the curves are not parallel over their entire length, the differences in ED_{50} cannot easily be tested by statistical means. It is further to be noted that the response curve associated with irradiation at nine days of gestation shows a threshold value of about 60 r, whereas there seems to be no threshold when a preliminary treatment is given three days earlier. Considering the curves only at the estimated ED_{50} level, there is a 48 r shift toward lower doses after a sensitizing exposure of 110 r at six days. This implies that 44 per cent of the earlier irradiation is effective after an interval of three days to enhance the effects of the second exposure.

The effects of this procedure have also been considered in terms of the percentage of fetuses showing microphthalmia somewhat less severe than that shown in Figure 1*B*. The two dose-response curves shown in Figure 4 are seen to have approximately the same shape. They may be shown to be parallel with greater than 95 per cent probability, although on inspection there seems to be a tendency toward increased slope for the curve resulting from preirradiation at six days. The ED_{50} of 93 r and 79 r for irradiation at nine or at six plus nine days, respectively, is significantly different at the 95 per cent confidence level. The curve obtained after a preliminary exposure at six days shows a 14 r displacement to the left. This would imply that only about 13 per cent of the first exposure remains effective for sensitization, which is somewhat less than that found for reduction in the size of the mandible. It is of interest to note, however, that the curves both show a threshold and that this, if it is shifted at all by the preliminary exposure at

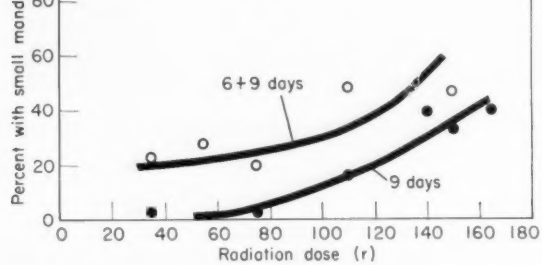

FIG. 3. Incidence of mandibular shortening produced by irradiation at nine days of gestation with and without pretreatment at six days.

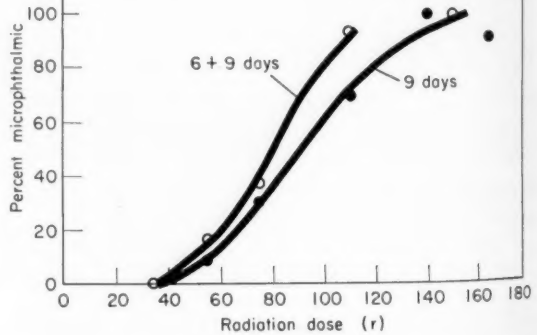

FIG. 4. Incidence of microphthalmic embryos after irradiation at nine days of gestation with and without pretreatment at six days.

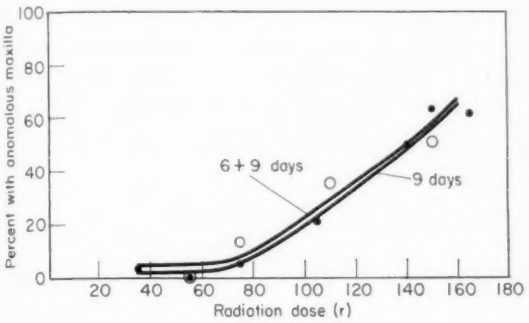

Fig. 5. Percentage of embryos with anomalies of maxillary development after irradiation at nine days of gestation with and without pretreatment at six days.

six days, is altered only by a very small amount.

The elements composing the maxilla are completely fused by the end of the fourteenth day of gestation in the normal fetus as shown in Figure 1, *A* and *C*. The degree of nonfusion indicated in this diagram was, for our purposes, considered to be anomalous. The curves of the percentage of fetuses showing this degree of incomplete fusion as a function of dose are shown in Figure 5. As will be noted, the slopes and ED_{50} are essentially the same whether or not a sensitizing exposure is given at six days. It would thus seem that treatment at six days does not influence the amount of maxillary damage produced by subsequent irradiation at nine days.

Abnormalities of the limbs, as well as malformations of the head such as microcephaly, blebs, and encephalocoele were seen in many of the fetuses. These anomalies were produced by lower doses of radiation when a sensitizing dose of 110 r was given at six days rather than when irradiation was administered at nine days alone. These changes were seen only at higher doses so that the data were insufficient to analyze quantitatively.

DISCUSSION

It is apparent from the results obtained in this experiment that an exposure to roentgen radiation at six days of gestation, which is itself without gross effect, potentiates the effect of a second exposure at nine days of gestation. On this basis it would seem that changes do occur in the six day embryo which are morphologically undetectable by usual techniques. These changes, which do not become apparent even at very high doses, remain for at least three days and are able to increase the magnitude of the response to additional radiation administered at that time. Since this effect is not detectable except through the use of additional radiation at some later time, it may be regarded as a sensitization process. The importance of this process, in terms of the production of certain malformations, is seen to be sufficiently great to account for the findings in our earlier experiments with radioactive phosphorus. It may thus be concluded that the small residual amounts of radioactivity remaining at nine days after injection of P^{32} at six days of gestation may be responsible for malformation production in an embryo sensitized by the earlier exposure.

It is not possible at this time to offer any explanation of the mechanisms involved in the sensitization to the production of malformations. This phenomenon poses less problems in terms of the lethal effect, since embryonic death can be produced by exposure at six days with doses slightly higher than those here used for sensitization. Although more detailed knowledge of the alterations leading to death would be required to decide whether or not the sensitization phenomenon was comparable to that operating in the case of the use of the divided dose technique for the study of recovery in the adult, it is felt that the two are akin.

The fact that the shift of the curves toward lower doses is in all cases less than the administered 110 r is of importance. When it is considered in the light of the uncertainty about the mechanisms involved, it gives rise to the possibility that recovery from the effect of the first radiation dose occurs in the three days between exposures. Insufficient information is available to choose between this possibility and

the alternative that the sensitization process is incomplete. If we assume a logarithmic relation for recovery from the lethal effects, as is found in the adult, the recovery rate may be quantitated. On this basis, a half-recovery time of 1.7 days would be obtained which is distinctly less than that found in the adult animal.

When this rate is compared with the series of recovery half-times for the lethal effect in adult animals, as presented in the review by Davidson,[1] relations of particular interest may be noted. He found, on compiling the available data, that recovery half-time was inversely proportional to the size of the animal. It is not known whether this is a phenomenon associated with size *per se*, since other parameters such as life expectancy, basal metabolic rate, and the average life of certain radiosensitive cells follow the same order within the series. Of importance, however, is the fact that we have obtained an estimated value of 1.7 days as the recovery half-time in the rat embryo, which is distinctly less than the range of values of three to eight days in the adult mouse and six to nine days in the adult rat. This presents the added possibility that recovery rate may also be related to the degree of differentiation of a tissue or to the general level of undifferentiated cells in an organism.

Clinically, it would be of certain great importance to know which of these possibilities are in fact responsible for the characteristic recovery rate. If it were to be found to be related to some one variable that could be manipulated under clinical conditions, it might be possible to increase the differential in recovery rate between normal and neoplastic tissue and thus effect more satisfactory radiation therapy.

The fact that a preliminary exposure at six days of gestation may produce a shift in the threshold or in the slope of a dose-response curve is of interest. There is the likelihood that such a relation of slope and threshold changes may pertain in the case of both normal and neoplastic tissues in the human. This would, of course, become most complicated in the case of multiple irradiations since it would imply a continuous change in these factors. Such a phenomenon would, however, have pronounced clinical value if it were definitely demonstrated to occur and was sufficiently well studied to be completely understood.

SUMMARY

Pregnant female rats were subjected to a preliminary exposure of roentgen rays at six days of gestation and again irradiated with a variety of doses at nine days. The results of such exposure, expressed in terms of embryonic mortality, growth, and abnormalities, were compared to the damage produced by a single exposure at either six or nine days.

It was found that a 110 r preliminary exposure dose reduced the LD_{50}, determined as the dose required to kill 50 per cent of the embryos by fourteen days of gestation, from 147 r to only 115 r. Pretreatment at six days with a second exposure at nine days also served to eliminate the threshold usually seen with single exposures from the dose-response curve. Similar results were obtained when weight depression was studied.

The dose of radiation at nine days of gestation required to obtain mandibular shortening in 50 per cent of the fetuses was markedly decreased by a previous exposure at six days. This treatment also significantly decreased the dose required to obtain eye changes. Pretreatment was not effective in increasing the incidence of maxillary changes.

The data obtained in these experiments have been interpreted as indicating that a sensitization of the embryo occurs which enhances the teratogenic effects of later radiation exposures. It was also found that recovery from certain of such effects may occur and at a rate greater than that found in the adult rat. These findings may be shown to have ultimate clinical importance.

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STRAY RADIATION FROM THERAPEUTIC ROENTGEN-RAY BEAMS*

By A. F. HOLLOWAY, PH.D.
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THE problem of radiation scattered to the side of a patient undergoing roentgen therapy may be of considerable importance when computing the protection requirements of a therapy room. Information about the quantity and quality of scattered radiation is available for the energy range 60 kv. to 100 kv.[1,6] and for Co^{60} radiation.[3] However, for the other energies, the convention normally adopted is that the scattered radiation measured at 1 meter from the scatterer does not exceed 0.1 per cent of the incident beam. [2,8]

In part A of this paper an experiment is described to test the validity of this contention for roentgen rays generated at voltages between 150 kv. and 250 kv. In part B an attempt is made on the basis of single scattering to account for the observed results.

(A) EXPERIMENTAL DETERMINATION OF SCATTERED RADIATION

EXPERIMENTAL ARRANGEMENTS

The experiments were performed by measuring the scattered dose at a point 40 cm. to one side of a phantom (Fig. 1). A water phantom 30 cm.×30 cm.×20 cm deep was irradiated by a beam of roentgen rays one edge of which was parallel to the side of the phantom. The distance from the target to the phantom surface was 50 cm. Most of the measurements were made with the edge of the beam coincident with the edge of the phantom; however, a shell of water of varying thickness was interposed between the edge of the beam and the edge of the phantom for part of the experiment to determine the shielding effect of the phantom material.

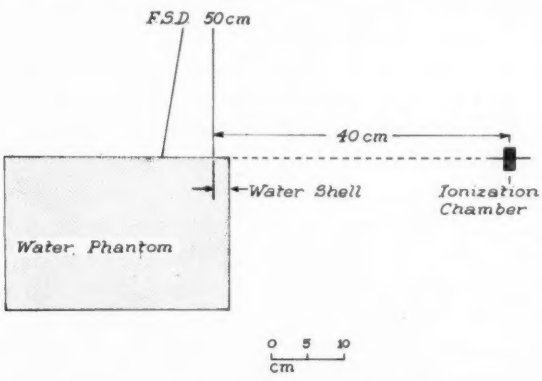

FIG. 1. Experimental arrangement illustrating the water shell.

In order to protect the measuring chamber* from the main beam, additional lead shielding was required around the tube head.

The experiments were carried out by exposing the surface of the phantom to 100 r incident air dose for various quality roentgen rays and measuring the amount of scattered radiation to one side of the phantom. This measurement was performed at 40 cm. for all experiments except one in which the dependence of scattered dose rate on distance was investigated by making the measurements at several distances from the edge of the phantom varying from 9 cm. to 56.4 cm.

Additional experiments were carried out to measure the variations in scattered dose as the field size was varied and also as the thickness of the water shell between the edge of the field and the edge of the phantom was varied.

RESULTS

The results of the experiments are shown

* The scattered dose was measured using ionization chambers of the M.R.C. design type B.D. 11, manufactured by the Baldwin Instrument Co. These chambers are stated by the manufacturer to be substantially independent of quality for gamma rays and all roentgen rays above 0.1 mm. Cu half value layer.

* From the Ontario Cancer Treatment and Research Foundation, Kingston Clinic, Kingston, Ontario, Canada. This paper was read, in part, at the Ninth International Congress of Radiology in Munich.

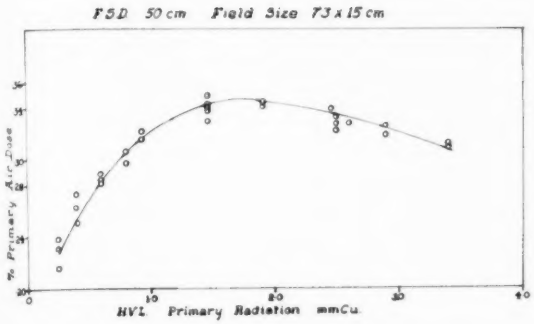

Fig. 2. Relation between the scattered dose, expressed as a per cent of the primary air dose, and the quality of the primary radiation.

in the following figures. Figure 2 shows the amount of scattered radiation 40 cm. to one side of the field in terms of per cent primary air dose for primary radiation of quality 0.35 mm. Cu to 3.40 mm. Cu. These results were obtained with no water shell between the edge of the beam and the ionization chamber. Figure 3 shows the variation in dose as a water shell is placed adjacent to the field edge in the path of the scattered radiation. From these graphs it may be seen that, at a position 40 cm. to one side of the scattering medium, the dose rate is approximately 0.3 per cent of the primary air dose rate. If a water shell of 10 cm. thickness is interposed between the edge of the field and the ionization chamber, one observes from Figure 3 that the dose rate is only reduced by a factor of one-half.

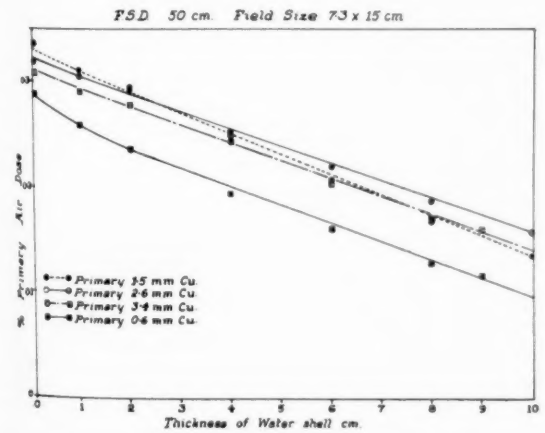
F.S.D. 50 cm. Field Size 7.3 x 15 cm.
% Primary Air Dose
Primary 3.5 mm Cu.
Primary 2.6 mm Cu.
Primary 3.4 mm Cu.
Primary 0.6 mm Cu.
Thickness of Water shell cm.

Fig. 3. Relation between side scatter and thickness of the water shell.

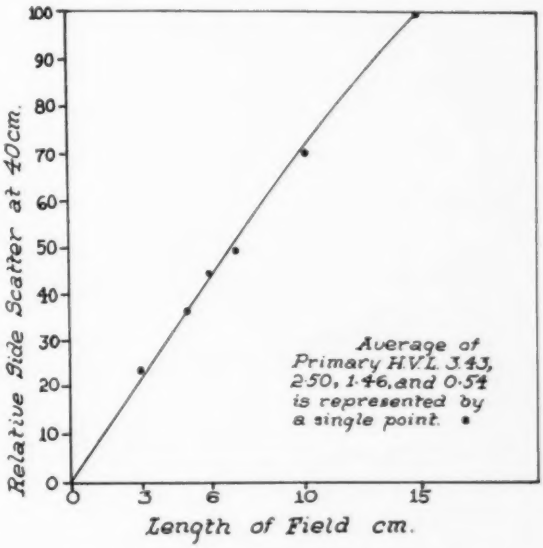
Relative Side Scatter at 40cm.
Average of Primary HVL 3.43, 2.50, 1.46, and 0.54 is represented by a single point.
Length of Field cm.

Fig. 4. Relation between side scatter and length of the field.

The results given above were obtained using a field area of 7.3 cm. × 15 cm. on the surface, the 15 cm. dimension being parallel to the phantom edge nearest the chamber. Figures 4 and 5 show the variation in scattered dose as the length and width of the field are varied. Figure 4 shows, as one would expect, that the amount of scatter to one side of a field varies almost directly with the length of the field, this relation falling off slightly for larger fields. The scattered dose also depends on the width of the field, as shown in Figure 5, but absorp-

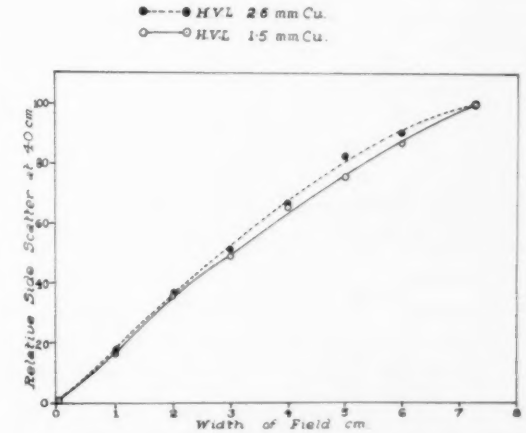

Fig. 5. Relation between side scatter and width of the field.

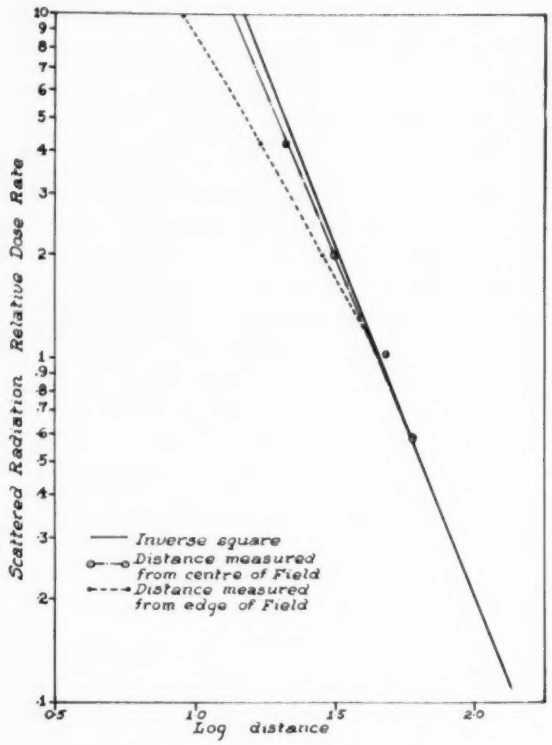
Scattered Radiation Relative Dose Rate
Log distance
Inverse square
Distance measured from centre of Field
Distance measured from edge of Field

FIG. 6. Variation of side scatter with distance from the scattering medium.

tion in the phantom plays an increasing role as the width increases.

Measurements were made at various distances from the edge of the phantom in order to find whether the scattered dose rate did, in fact, fall off as the inverse square.

The results of this investigation are shown in Figure 6. The solid line in the figure denotes an inverse square relation. The middle curve shows experimental results when the distance was measured from the centre of the field; the lower curve gives the results when the distance was measured from the near edge of the field. It is seen from this figure that the variation in dose rate follows the inverse square law even down to the distances as short as 15 cm. from the centre of the field. The data for this curve were obtained using primary roentgen rays of qualities ranging from 0.54 mm. Cu to 3.4 mm. Cu half value layer.

Finally, an attempt was made to measure the quality of the scattered radiation. This was done by placing large sheets of copper over the side of the phantom and measuring the half value layer. While these measurements were not carried out using "good" geometry, they are at least an indication of the quality of the scattered radiation. The results of this investigation are shown in Figure 7. All primary beams with the exception of the 0.35 mm. Cu half value layer were produced by a roentgen-ray machine operating at 250 kv. The other point was obtained using roentgen rays generated at 150 kv. The points shown in Figure 7 were all measured with no water shell between the edge of the field and the edge of the phantom, with the exception of two points shown as solid circles for primary half value layers of 1.5 mm. Cu and 2.5 mm. Cu where additional measurements were made using a water shell 10 cm. thick. As seen from the graph, there was no significant change in the quality of the scattered radiation when this water shell was placed between the edge of the field and the ionization chamber. The half value layer of the scattered radiation, for the qualities investigated, is approximately one half of the primary radiation, tending to be harder than this at low energies and softer at high energies.

CONCLUSION

The conclusion which may be drawn from the results reported above is that, for roentgen-ray beams with a half value layer between 0.35 mm. Cu and 3.5 mm. Cu, the scattered dose one meter from the centre of

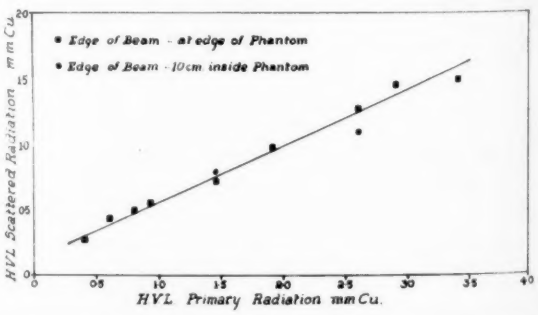
Edge of Beam - at edge of Phantom
Edge of Beam - 10cm inside Phantom
HVL Scattered Radiation mm Cu
HVL Primary Radiation mm Cu

FIG. 7. The quality of the scattered radiation is plotted against that of the corresponding primary.

the beam and the patient, measured in a direction at right angles to the incident beam, is less than 0.1 per cent of the primary air dose delivered to the patient. The scattered dose was found to vary approximately as the area irradiated and the dose delivered to any point at right angles to the main beam will vary inversely as the square of the distance from the centre of the primary field to the point of measurement. Further, one may conclude that the half value layer of the scattered radiation is approximately one half that of the primary beam. As one would expect, the scattered radiation is somewhat softer at higher energies and harder at lower energies than the simple approximation referred to above. The quality of scattered radiation from a phantom irradiated by roentgen rays generated at 100 kv. peak (half value layer 0.8 mm. Al) was also investigated. Here the scattered radiation was found to have a quality of 4 mm. Al when an 8 cm. thick water shell was placed between the edge of the beam and the ionization chamber. This compares with a value of 2.9 mm. Al found by Keane and Spiegler[6] when the water shell was only 3 cm. thick.

(B) CALCULATION OF SCATTERED RADIATION

INTRODUCTION

Consider a parallel roentgen-ray beam $7\frac{1}{2}\times 15$ cm., instead of one diverging with focal source distance of 50 cm. as used in the experiment, impinging on the water phantom. This assumption should make little difference in the results. Consider also the single 90° scattering case as a first approximation (Fig. 8).

CALCULATION

Let D_λ be the dose rate at $P(x.y.)$ due to wave lengths between λ and $\lambda+d\lambda$ in the primary beam. Let the dose rate at P corresponding to D_λ in the absence of the phantom be $I_{0\lambda}$ r/min. Note that $I_{0\lambda}$ will not vary with x since we are considering a parallel beam.

Then $D_\lambda = I_{0\lambda}e^{-\mu x}$ where μ is the linear absorption coefficient for wave length λ.

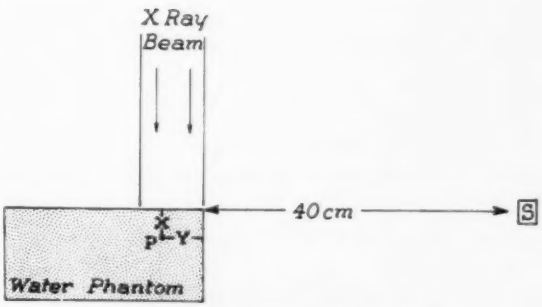

FIG. 8. Assumed geometry for theoretical consideration.

D_λ, however, is due to N_λ, the number of photons with wave length between λ and $\lambda+d\lambda$.

$$N_\lambda = \frac{10^9 \cdot D_\lambda E_\lambda}{1.6 \cdot 12.40/\lambda}$$

$$= 4.98 \times 10^7 D_\lambda E_\lambda \lambda \text{ photons cm.}^{-2}\text{sec.}^{-1}$$

where E_λ[5] is energy flux per roentgen for wave length λ and $d\lambda$ is measured in ångstroms. Now some of N_λ will be scattered through 90° and the number of these passing through each square centimeter at 40 cm. distance is:

$$N_{\lambda'} = N_\lambda n_0 \frac{d\sigma}{d\Omega} \frac{1}{(40+y)^2} e^{-\mu' y} dV,$$

where

$$dV = 15 \cdot dx \cdot dy.$$

n_0 is the number of electrons per gram for water phantom and μ' is the linear absorption coefficient for scattered radiation.

$d\sigma/d\Omega$ is the differential Klein-Nishina cross-section[7] for the number of photons scattered through 90° per unit solid angle per electron.

∴ Number of photons of wave length λ scattered through 90° and reaching S is $N_{s\lambda'}$

$$N_{s\lambda'} = \int\int 4.98 \cdot 10^7 \cdot E_\lambda \lambda I_{0\lambda} e^{-\mu x} n_0 \frac{d\sigma}{d\Omega} \frac{15}{(40+y)^2} \cdot e^{-\mu' y} dx \cdot dy \text{ photons cm.}^{-2} \text{ sec.}^{-1}$$

where the primes refer to scattered radiation.

∴ Dose rate at S

TABLE I

μ'	$X \times 10^3$
.14	2.57
.17	2.34
.20	2.20
.25	1.91

$$S_{\lambda'} = \frac{N_{s\lambda'} \cdot 12.40/\lambda' \cdot 1.6 \cdot 10^{-9}}{E_{\lambda'}}$$

$$= 2.01 \cdot 10^{-8} \cdot \frac{N_{s\lambda'}}{\lambda' E_{\lambda'}} \text{ r/min.}$$

On substituting the appropriate values, this last equation reduces to:

$$S_{\lambda'} = I_{0\lambda} n_0 \frac{d\sigma}{d\Omega} \frac{\lambda}{\lambda'} \frac{E_\lambda}{E_{\lambda'}} \frac{15}{\mu} \int_0^{7.5} \frac{e^{-\mu' y}}{(40+y)^2} \cdot dy \text{ r/min.}$$

since $n_0 d\sigma/d\Omega$ is constant for a given wave length and angle of scatter. The remaining integral may be solved graphically. Calling this integral X, its value, found by graphical integration for various values of μ', is given in Table I.

Now let us use the above expression to calculate the spectrum (and amount) of scattered radiation from a phantom irradiated by 250 kv. (half value layer 2.6 mm. Cu) roentgen rays. The spectrum of the primary radiation as determined by Greening's method[4] is shown in Figure 9.

The values of $S_{\lambda'}$ versus λ' found by the calculation outlined above are also shown on Figure 9 with a dotted curve. Taking values from this graph, we may calculate the penetration through Cu filters of 0.5 mm., 1.0 mm., and 1.5 mm. thicknesses, respectively. These spectra lead to a calculated half value layer for the scattered radiation of 1.5 mm. Cu. Experimentally, the half value layer was found to be 1.2 mm. Cu. By experiment, the scattered dose rate at 40 cm. to one side of the field was 0.33 per cent of incident air dose, whereas the above calculation gives a figure of 0.16 per cent. The above calculations were repeated with two other spectra, and the results are summarized in Table II.

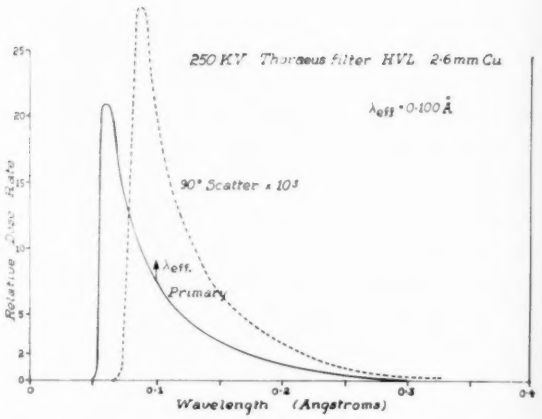

FIG. 9. Calculated primary and scattered spectra for 250 kv. roentgen rays.

The primary and secondary spectra for these two additional half value layers are shown in Figures 10 and 11, respectively.

CONCLUSION

The results of our simple single scattering theory are seen to be quite sufficient to

TABLE II

Primary Beam		90° Scattered Radiation			
kv.	Half value layer	Half value layer		Dose rate (per cent of primary)	
		Experimental	Calculated	Experimental	Calculated
250	2.6 mm. Cu	1.2 mm. Cu	1.5 mm. Cu	0.33	0.16
200	1.0 mm. Cu*	0.57 mm. Cu	0.65 mm. Cu	0.32	0.17
100	0.8 mm. Al	4.0 mm. Al†	2.7 mm. Al	0.05†	0.046

* 15 per cent characteristic radiation.
† This value was obtained with an intervening water shell 8 cm. thick and with a focal skin distance of 20 cm.

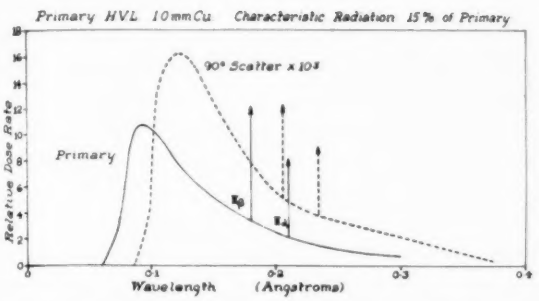
Primary HVL 1.0 mm Cu Characteristic Radiation 15% of Primary
90° Scatter x 10³
Primary
Relative Dose Rate
Wavelength (Angstroms)

Fig. 10. Calculated primary and scattered spectra for 200 kv. peak roentgen rays.

explain the large differences in wave length of the primary and scattered radiation. Quantitatively, however, single scattering would appear to account for only about one-half of the total quantity of radiation which is scattered to a point to one side of the beam.

SUMMARY

The first part of this paper describes an experiment to measure the quantity and quality of radiation scattered through 90° from a water phantom, which was irradiated by incident radiation whose quality was varied from 0.35 mm. Cu to 3.4 mm. Cu. The shielding effects of a water shell between the edge of the beam and the edge of the phantom were investigated as well as the variation in scattered dose rate with field size and distance from the scattering material.

In the second part of the paper the quantity and quality of scattered radiation are calculated on the basis of single scattering only and the results of these calculations are compared with the experimental results obtained in the first part.

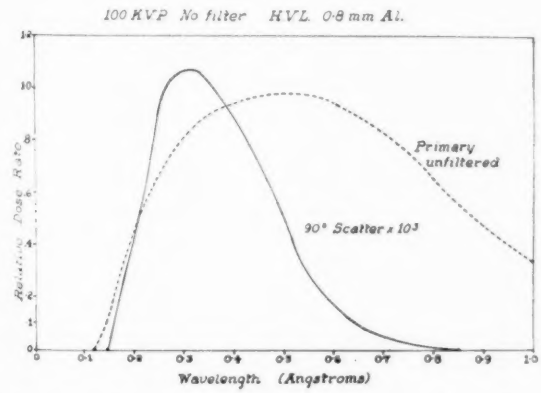

Fig. 11. Calculated primary and scattered spectra for 100 kv. peak roentgen rays.

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ROENTGEN REGRESSION IN AXOLOTL (SIREDON MEXICANUM)*

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THIS study is a review of all data concerning the phenomenon of regression, resorption, or reduction, which was observed after local irradiation of young or adult axolotl in our various investigations. This phenomenon was first reported more than twenty years ago[5,6,8] and in the following years some new observations were made concerning this problem. In 1950 the reduction of connective tissue and pigment cells during the primary acute reaction in irradiated tail of young axolotl was described;[9] in 1952, the resorption of teeth in young axolotl;[16] in 1954, the reduction of pigment cells in the irradiated anterior portion of the head of young axolotl;[11] in 1958, the resorption of the lens in the eye of young axolotl;[15] and in 1959, the resorption of teeth in adult axolotl.[14] All these data are summarized in this paper along with some previously unpublished data.

Primarily, this paper reports an investigation of the most typical phenomena in the reaction of limb regenerates of adult axolotl to irradiation. This study is a repetition of earlier work and was done to verify our earlier conclusions concerning the resorption process.

MATERIALS AND METHODS

Forty-four adult axolotls, four to five years old, of different strains were used. The hind limbs of all animals were amputated in the femoral region. At the time of irradiation, 79 days later, the regenerated limbs were 9–12 mm. long and possessed 4 toes. The right hind limb regenerates of 22 animals were irradiated locally with 4,000 r and those of 12 animals with 6,000 r; the left hind limb regenerates served as nonirradiated controls. Ten animals served as additional untreated controls.

The irradiation was carried out at 100 kv., 30 ma., 1 mm. Al filter, beryllium window tube, half-value layer of 2.0 mm. Al, intensity of 410 r/min. in air, and a target object distance of 18 cm. Before irradiation the animals were anesthetized with a weak aqueous solution of tricaine methanesulfonate (M.S. 222) and then held in a coiled position by an elastic bandage so that only the right hind limb was free. The right hind limbs of 4 animals were irradiated simultaneously. The bodies of the animals were shielded with a 4 mm. lead sheet having a radiation localizer 6.5 cm. in diameter.[10] Immediately after treatment, the animals were put into water, where they recovered from the anesthesia. For histologic study, the limbs were fixed in acetic mercuric chloride formalin (Stieve). The material was embedded in paraffin with 5 per cent beeswax and sectioned at 8–10 microns. The sections were stained with Ehrlich's hematoxylin and eosin, and photomicrographs were taken of different areas at various magnifications.

THE NORMAL PROCESS OF REGENERATION

Among the Amphibia, the Urodela (newts, axolotls, salamanders, etc.) are able to restore limbs, tail, and parts of the head following injury or amputation. As soon as bleeding stops, the healing process begins. The initial epidermal healing of the wound is accomplished by a migration of epidermal cells or by migration of the epidermal layer from adjacent regions. This occurs without extensive mitotic activity (Korschelt, 1927). The healing of

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the wound is a separate process which is not related to the regenerative ability. In animals which possess the ability to regenerate, it is manifest only after the wound is completely healed. Regeneration begins only under suitable conditions; it cannot begin, for example, in the absence of a freshly healed wound.

The process of regeneration starts with resorption of the damaged tissue at the site of amputation. The giant wandering cells phagocytize all distal portions of the tissues, all damaged cells, dead blood cells, etc. Immediately thereafter, in the distal portion of the amputated limb, accumulated mesenchymal cells begin to divide rapidly, forming the anlage of the new regenerate, the regeneration blastema (Korschelt, 1927). After the regeneration blastema is formed, a period of more rapid regeneration with progressing tissue differentiation is observed. Usually, within two or three months after amputation, a full-sized limb with 5 digits is formed in adult newts (Triton cristatus) and in adult axolotls (Siredon mexicanum).[4] Regeneration is a rapid morphogenetic process and the missing organ may be restored in one-fourth or one-fifth of the time required for normal ontogenetic development.

RESULTS OF MICROSCOPIC INVESTIGATION OF TISSUES OF LIMB REGENERATES UNDERGOING REDUCTION

Thirty-three hind limb regenerates were studied histologically. Twenty had been irradiated with 4,000 r and 13 with 6,000 r. All conclusions concerning tissue damage and percentage frequency of tissue damage were derived from this material.

SKIN EPITHELIUM AND SUBCUTANEOUS PIGMENT LAYER

In general, changes in the skin epithelium are important for an evaluation of the irradiation effect.[12] During regression of the limb, the skin epithelium appeared greatly reduced. The surface area of epithelium of regenerates with 4 toes was many times greater before reduction than the corresponding surface area of the small remnants of regenerates without toes which remained after reduction. Gradual reduction of the skin epithelium without the formation of open wounds was typical. The reason for this reduction remains obscure.

The appearance of the skin epithelium depended upon the interval between irradiation and fixation. With early fixation (45–80 days after irradiation) epithelial damage was evident in 70 per cent of the animals irradiated with 4,000 r and in 80 per cent of those irradiated with 6,000 r. Typical epithelial damage was the formation of giant cell degenerating epithelium, usually observed during the primary acute reaction.[7,8,9,15] A comparison of such epithelium (Fig. 1, 3 and 4) with the normal epithelium of control animals (Fig. 2) showed that in irradiated epithelium the cells and nuclei were two or three times larger. Abnormal epithelium in some cases had irregular outer and inner surfaces and some of the epithelial giant cells were isolated from the epithelium and had penetrated into subepithelial loose connective tissue (Fig. 1). The number of cell layers was reduced in most cases. As a result, only one layer of giant cells (Fig. 3 and 39) or occasionally two layers of cells (Fig. 5) were seen. In comparatively rare cases, in spite of the giant size of the cells, the number of cell layers was almost normal (Fig. 4).

In 12 per cent of animals, fixed 124–126 days after irradiation, typical giant cell epithelium was observed (Fig. 1). In all other animals fixed at this time, the epithelium appeared normal and was indistinguishable from that of controls (Fig. 30, 31 and 37). This condition corresponded to the secondary stable state.[9,15]

Our earlier opinion that epithelial reduction occurs as a result of the activity of giant macrophages, which produce the lytic enzymes in immediate proximity to the epithelial cells, is not confirmed by the present investigation. In spite of active degeneration of the epithelial cells, macro-

phages were rarely found in their immediate proximity. Giant cells, similar to macrophages, were sometimes noted near the lower layer of epithelium (Fig. 15), but we consider these cells to be modified giant epithelial cells, distinguishable from the typical macrophage (Fig. 14). Macrophages, on the contrary, were found near completely normal epithelium. Reduction of epithelium did not appear to depend upon the general process of resorption of the limb.

The number of pigment cells in normal skin varies. Separate pigment cells (Fig. 31) are sometimes found in either continuous subepithelial pigment layer. After irradiation, pigment cells were damaged in all cases; however, the degree of damage varied considerably. In rare instances the pigment cells disappeared completely (Fig. 37); in most there were isolated normal pigment cells (Fig. 30) and damaged cells without processes (globular form) nearby. The condition of the pigment cells did not depend upon the condition of the adjacent tissue. Normal pigment cells were found under degenerating giant cell epithelium and damaged cells under normal epithelium. The reaction of the pigment layer to irradiation may, like that of epithelium, be independent of the general process of limb reduction.

SKELETON

I. *Resorption of the Skeleton of Adult Animal.* After irradiation with 4,000 r, resorption of skeletal cartilage and bone was observed in 80 per cent of the animals with early fixation and in 100 per cent of the animals fixed 124–126 days later. After irradiation with 6,000 r, resorption of the skeleton was observed in 100 per cent of the animals at either time. This investigation confirmed our previous conclusions[4,8] that resorption of the limb skeleton is the result of the activity of macrophages.

In regenerates with four toes, which were studied in this investigation, a comparatively thin layer of bone usually covered both the proximal and distal portions of the cartilaginous skeletal element (Fig. 11). Sometimes, however, it covered only the proximal portion (Fig. 6) or the distal portion (Fig. 11). The attack of macrophages on the skeletal element always began at the surface and often at the distal or proximal end. Therefore, in most cases the peripheral bone layer was damaged first.

PLATE 1.

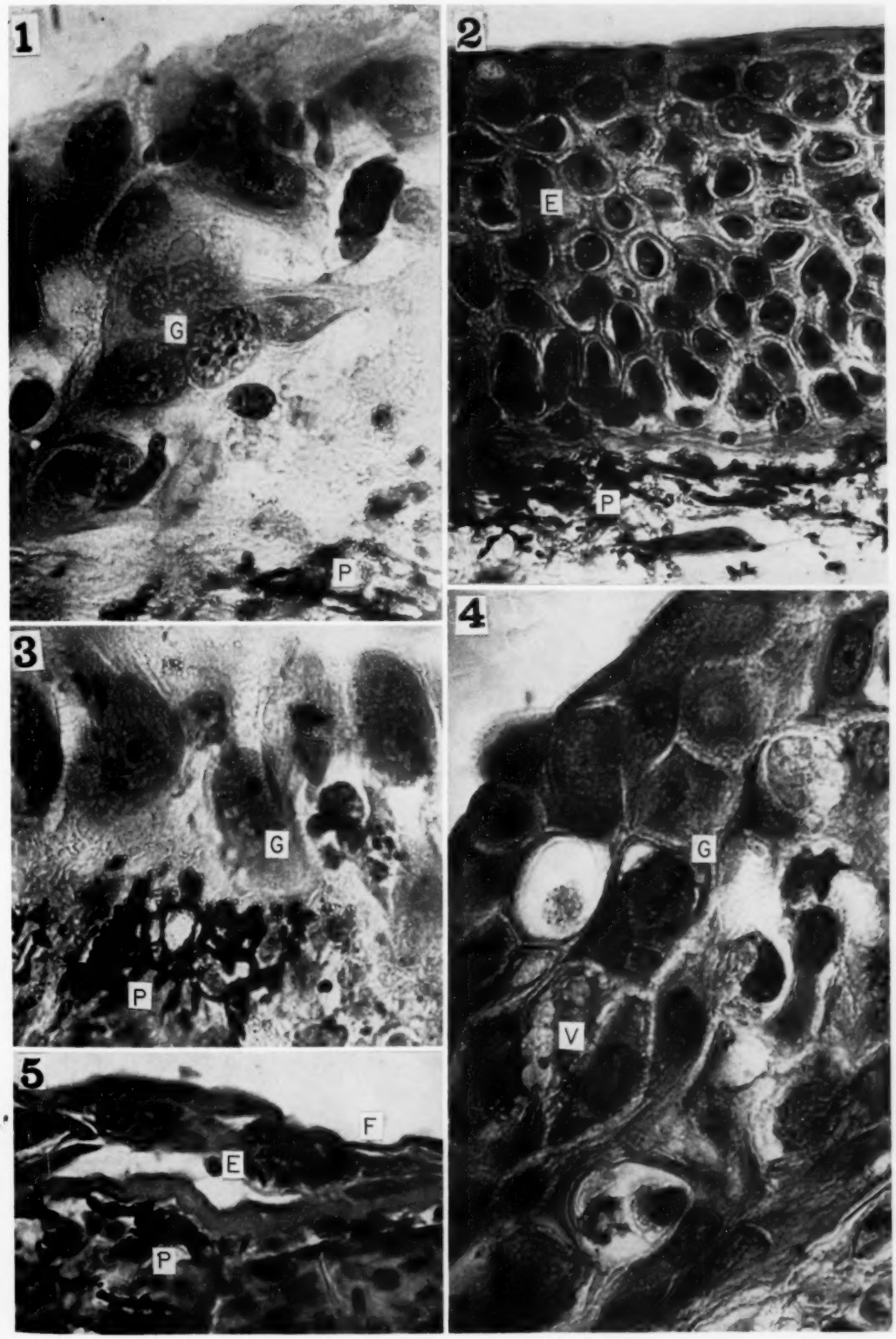
FIG. 1. Limb regenerate of axolotl (No. 16) 126 days after local irradiation with 4,000 r, showing abnormal skin epithelium. G—giant epithelium cells; P—pigment cells. Photomicrograph ×500.

FIG. 2. Limb regenerate of a control animal. E—normal epithelium cells; P—pigment cells. Photomicrograph ×500.

FIG. 3. Limb regenerate of axolotl (No. 17) 63 days after local irradiation with 4,000 r, showing abnormal skin epithelium. G—giant epithelium cells; P—pigment cells. Photomicrograph ×500.

FIG. 4. Limb regenerate of axolotl (No. 27) 63 days after local irradiation with 4,000 r, showing abnormal skin epithelium of great thickness. G—giant epithelium cells; V—vacuoles in protoplasm of epithelial cells. Photomicrograph ×500.

FIG. 5. Limb regenerate of axolotl (No. 12) 64 days after local irradiation with 4,000 r, showing abnormal epithelium consisting of only two layers of cells. E—lower layer of giant cells; F—exterior layer of flat cells; P—pigment cell. Photomicrograph ×500.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The degree of damage depended on the number and size of macrophages accumulated in any particular area. In some cases, many macrophages were crowded in one place and the bone layer was completely destroyed on one side, but hardly damaged on the other (Fig. 6 and 7). In exceptional cases the bone layer disappeared completely in the early stages of skeletal resorption. Wherever there was bone or cartilage damage, macrophages were located in close proximity to the bone surface (Fig. 7 and 8). The cavities and holes in the bone or cartilage resulted from the action of lytic enzymes secreted by macrophages (Fig. 6 and 9). In some cases the exterior bone layer was only partially damaged. After a hole was formed in the bone layer, macrophages were able to penetrate into the cartilage. In such cases the bone layer temporarily remained almost intact, having only a few small cavities (Fig. 10), while almost all the cartilage within was dissolved. Apparently, the intercellular substance of cartilage was rapidly dissolved by macrophage enzymes. As a result, in some cases (Fig. 10) most of this substance disappeared, leaving isolated cartilage cells with large macrophages between them. Through phagocytosis, apparently, engulfed cartilage cells appeared within the macrophages as inclusions (Fig. 10). In some cases the distal skeletal elements were normal (Fig. 12), while the more proximal elements were undergoing reduction (Fig. 13). In the early stages of reduction, only a few macrophages were attached to the surface of the cartilage element, which was practically undamaged (Fig. 6). The appearance of skeletal cartilage undergoing reduction (Fig. 10 and 13) was in great contrast to that of the normal cartilage of a control animal or the undamaged cartilage of the same animal (Fig. 11 and 12). In cartilage undergoing reduction, the number of cartilage cells was greatly decreased (Fig. 13 and 20). Probably most of these cells were phagocytized by macrophages, since macrophages were typically present in close contact with the cartilage and penetrating into it (Fig. 13 and 20). The marcophages varied in size and activity. Giant macrophages were comparatively rare and never penetrated deeply into the cartilage element. These macrophages and those of medium size were the most active phagocytes. The smallest macrophages, only three or four times larger than carti-

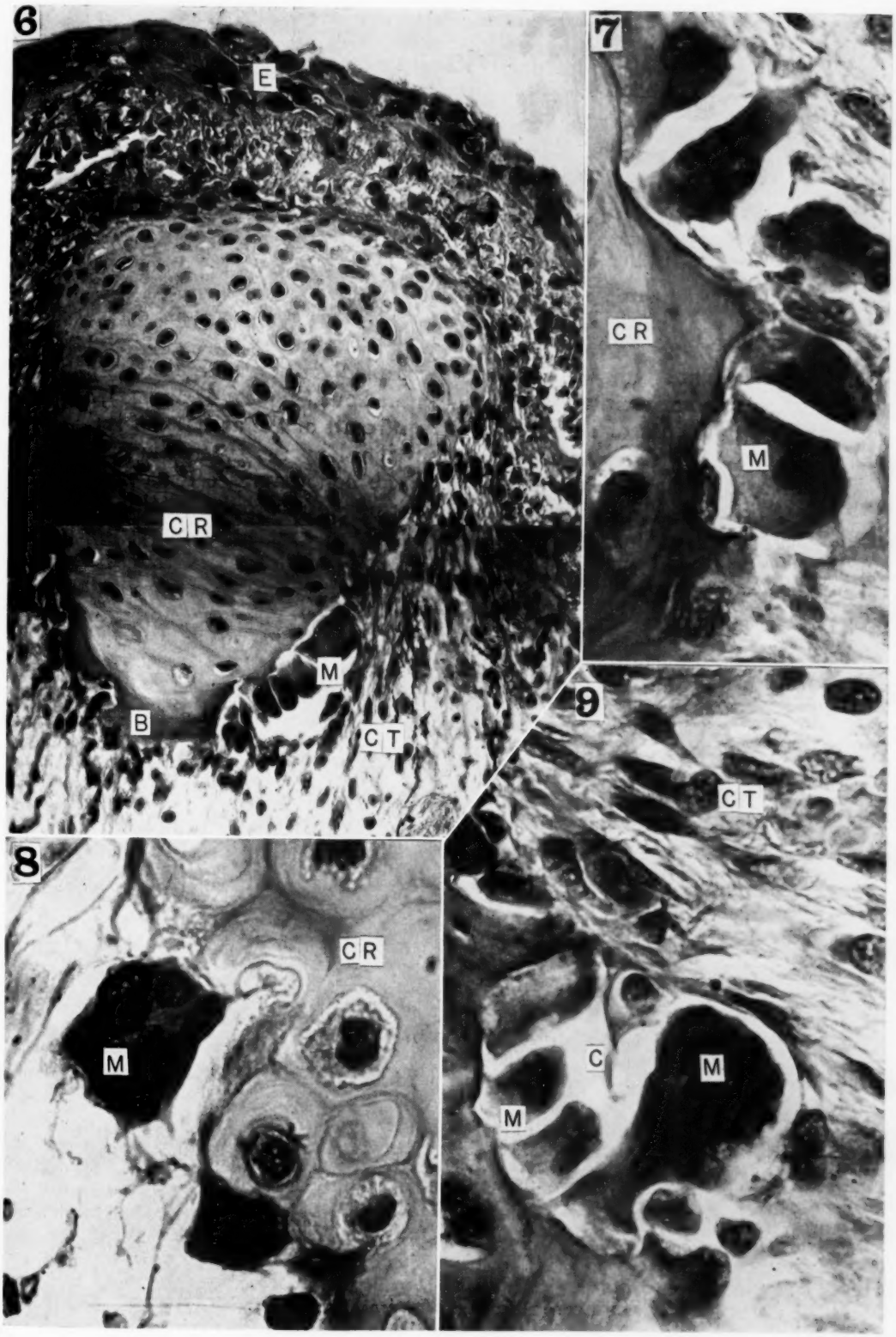
PLATE II.

FIG. 6. Limb regenerate of axolotl (No. 27) 63 days after local irradiation with 4,000 r, showing the beginning of reduction of the skeletal element. B—proximal layer of bone damaged in several places by macrophages; CR—cartilaginous tissue of skeletal element; CT—loose connective tissue; E—skin epithelium; M—macrophages, which have dissolved the bone layer and are starting to penetrate into cartilage. Photomicrograph ×150.

FIG. 7. Part of the section through the limb regenerate of axolotl (No. 28) 126 days after local irradiation with 4,000 r. CR—cartilage; M—macrophages. Photomicrograph ×500.

FIG. 8. Limb regenerate of axolotl (No. 27) 63 days after local irradiation with 4,000 r. CR—cartilage; M—macrophages. Photomicrograph ×500.

FIG. 9. Limb regenerate of axolotl (No. 28) 126 days after local irradiation with 4,000 r. C—cavity formed in cartilage by macrophages; CT—connective tissue cells; M—macrophages. Photomicrograph ×500.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lage cells, penetrated deeply into the cartilage substance. They actively dissolved cartilage, because they were always located in the empty spaces formed in the skeletal element (Fig. 18). In other cases, small cavities were connected and transformed into one large cavity occupying almost the whole cartilage element (Fig. 13). Such spaces were never seen in normal cartilage tissue (Fig. 12 and 19). In some cases a few large macrophages penetrated into the cartilage, but they were almost inactive, because the cartilage was not dissolved and typical cavities were not found (Fig. 16 and 17). Resorption was not continuous in all cases; however, the cause of its interruption is not known. When resorption was complete, all macrophages disappeared.

II. *Resorption of the Skeleton of Young Animals.* In recent experiments (Brunst—unpublished), the posterior portions of the body of young axolotls were irradiated with 1,000 r 50 days after hatching. About two months later the tails and hind limbs of most animals were distinctly reduced. Histologic investigation of an animal fixed 130 days after irradiation showed clearly the destructive activity of macrophages in the tail undergoing reduction. Many of these giant cells were in close contact with various bone portions of the vertebrae (Fig. 22).

Under higher magnification, macrophages were seen penetrating the bone (Fig. 21, 24 and 25) and attached to the bone surface (Fig. 23). The bone substance was dissolved and a large cavity had formed in the bone (Fig. 21, 24 and 25), apparently as a result of the activity of lytic enzymes produced by the macrophages. The shape of the bone cavity often corresponded to that of the macrophages (Fig. 21 and 25), suggesting that such a cavity was formed under the influence of macrophage processes which produced the lytic enzyme. Many protoplasmic inclusions, either

→

PLATE III.

FIG. 10. Limb regenerate of axolotl (No. 27) 63 days after local irradiation with 4,000 r. B—exterior bone layer partially damaged by macrophages; C—cavity in bone layer, formed as a result of macrophage activity; CI—isolated cartilaginous nuclei left after both intercellular and intracellular substance have been dissolved; CR—cartilage, almost normal in appearance; H—hole in bone layer; M—macrophages. Photomicrograph ×150.

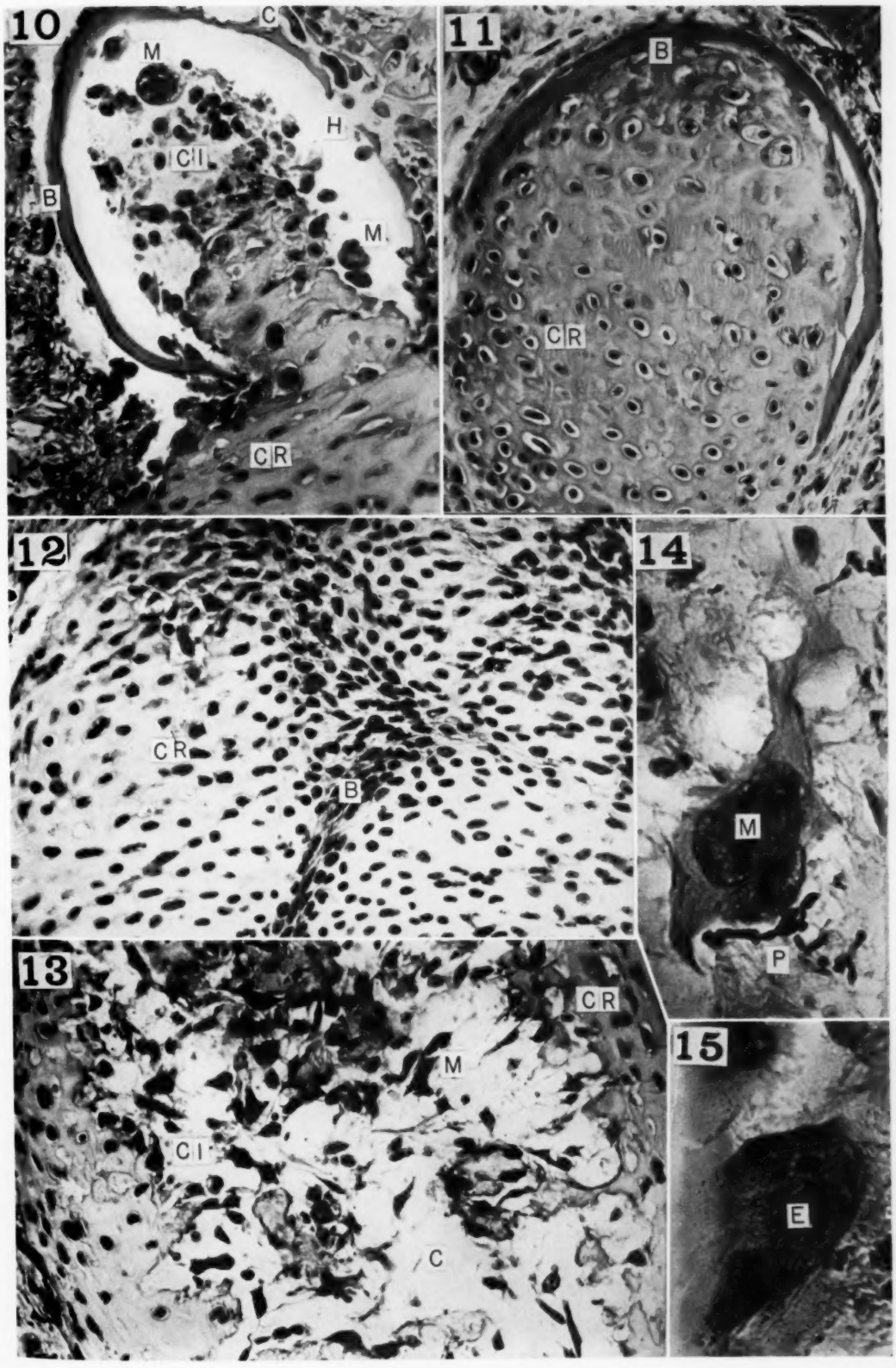
FIG. 11. Limb regenerate of a control animal. B—normal exterior bone layer; CR—normal cartilage. Photomicrograph ×150.

FIG. 12. Limb regenerate of axolotl (No. 13) 126 days after local irradiation with 4,000 r, showing distal portion of skeleton which appears normal. B—border between skeletal elements; CR—cartilage. Photomicrograph ×150.

FIG. 13. Limb regenerate of the same axolotl (No. 13) shown in Figure 12. This shows a more proximal portion of skeleton, which is greatly damaged. C—cavities in cartilage; CI—isolated cartilaginous cells; CR—cartilage which appears normal; M—macrophages. Photomicrograph ×100.

FIG. 14. Limb regenerate of axolotl (No. 13) 126 days after local irradiation with 4,000 r. M—giant macrophage in loose connective tissue; P—pigment cell. Photomicrograph ×500.

FIG. 15. Limb regenerate of axolotl (No. 17) 63 days after local irradiation with 4,000 r. E—giant epithelial cell from the lower layer of epithelium, resembling a giant macrophage. Photomicrograph ×500.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phagocytized connective tissue or cartilaginous cells, were found in these giant cells.

BLOOD VESSELS

Blood vessel damage was observed in 70–75 per cent of the animals that were irradiated with 4,000 r and in all animals irradiated with 6,000 r.

Early damage consisted of an increased number of small capillaries and vessels and an abnormal dilatation of the vessels. Advanced damage was characterized by the disappearance of the blood vessel walls with the formation of large sinuses, often immediately under skin epithelium.

Figure 29 shows a normal blood vessel; the endothelial cells are clearly seen. During the process of reduction, the distal portions of blood vessels gradually disappeared and, therefore, large blood vessels near the distal end of the limb were transformed into sinuses (Fig. 26). Many blood cells were observed in the connective tissue and an abnormally great accumulation of these cells was often seen in sinuses between the cartilaginous skeleton and epithelium (Fig. 27). The complete absence of endothelial cells was evident under higher magnification, in great contrast to the appearance of normal blood vessels (Fig. 28 and 29).

LOOSE CONNECTIVE TISSUE AND MUSCLES

Macrophages of various sizes were almost always found in the loose connective tissue, which has an important role in their distribution and spread. Through the connective tissue they can penetrate into the bone, cartilage, muscles, and other tissues and structures.

Some macrophages in loose connective tissue were small, being only twice as large as the connective tissue cells (Fig. 37). Others were three times as large as the connective tissue cells (Fig. 30, 31, 32 and 33), and in some places were accumulated in great numbers (Fig. 32). The largest macrophages, four to six times larger than connective tissue cells (Fig. 14 and 38), were found comparatively rarely and usually one or two such cells were isolated from the other macrophages.

During reduction, the amount of loose connective tissue and the number of connective tissue cells decreased greatly and was probably related to the activity of macrophages.

In some cases giant fibroblasts were noted (Fig. 44). Their appearance after total body irradiation with 6,000 r has already been described.[12] Apparently these cells were formed as a result of tissue reac-

PLATE IV.

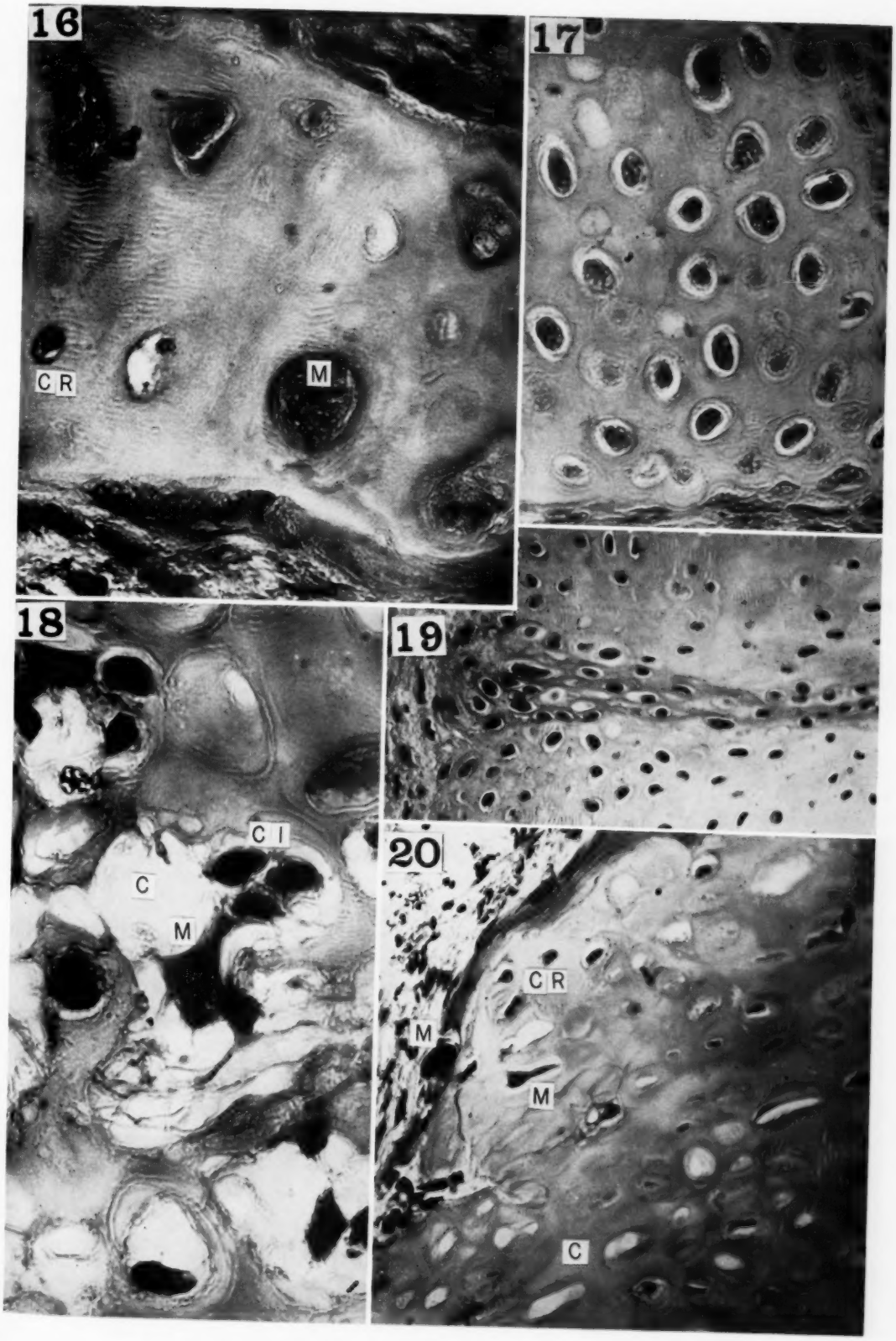
FIG. 16. Limb regenerate of axolotl (No. 21) 63 days after local irradiation with 4,000 r. CR—cartilage cell; M—inactive macrophage in the cartilage. Photomicrograph ×500.

FIG. 17. Limb regenerate of a control animal. Normal cartilage. Photomicrograph ×500.

FIG. 18. Limb regenerate of axolotl (No. 28) 126 days after local irradiation with 4,000 r. C—cavity in cartilage; CI—isolated cartilaginous cells; M—macrophages. Photomicrograph ×500.

FIG. 19. Limb regenerate of control animal. Normal cartilage. Photomicrograph ×150.

FIG. 20. Limb regenerate of axolotl (No. 7) 63 days after local irradiation with 4,000 r. C—cavity in cartilage; CR—cartilage cells; M—macrophage. Photomicrograph ×150.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C

tion to irradiation and were not related to the phenomenon of reduction.

Damage and disappearance of muscles were observed in 67 per cent of the animals fixed 63–65 days after irradiation with 4,000 r, and in all the animals irradiated with 6,000 r. In the process of reduction, compact muscle bundles (Fig. 34 and 41) were transformed into isolated small thin muscle bundles or even isolated muscle fibrils and separated nuclei. The appearance of muscle tissue undergoing reduction (Fig. 36) was in great contrast to normal muscle tissue (Fig. 34). Only separate, irregularly oriented, isolated muscle bundles and nuclei were seen. Between them macrophages were found. During more advanced reduction of this tissue (Fig. 35), only isolated muscle nuclei and remnants of muscle bundles, along with a great number of giant macrophages and many connective tissue cells, were found (Fig. 35 and 40). When muscle resorption was complete, the number of macrophages in that area also decreased.

The disappearance of muscles appeared to be related to the activity of macrophages and was probably the result of lytic enzymes secreted by these cells. Although actual phagocytosis was not observed, it is possible that muscle nuclei can be engulfed by macrophages. Inclusions found in the protoplasm of some macrophages appeared to be engulfed muscle nuclei (Fig. 40).

THE TEETH

The resorption of teeth of young axolotls irradiated with 2,000 r or 4,000 r 20 days after hatching and with 3,000 r 60 days after hatching has been described.[16] The teeth disappeared quickly. Forty-three days after irradiation, only small remnants of teeth were found, and within 10 days, even the remnants had completely disappeared. Some observations showed that macrophages play an active part in the destruction of the teeth in young animals.

The resorption of teeth of adult axolotls irradiated with 6,000 r has been described by us.[14] The teeth began to disappear about 50 days after irradiation and disappearance was usually complete within another 10 to 15 days. This process was the result of the activity of the macrophages. A new generation of teeth, much smaller and irregular in shape and position, then began to form. About 150 days after irradiation, almost all of these second generation teeth had disappeared, again as a result of the activity of the macrophages. Under the roots of some of the teeth, the macrophages were clearly seen (Fig. 42 and 43).

THE LENS

The resorption of lens 40–80 days after irradiation of the head of young axolotl with 3,000–6,000 r has also been described.[13] Serious damage was observed in 29 per cent of all irradiated animals. Dissolution of the lens fibers progressed gradu

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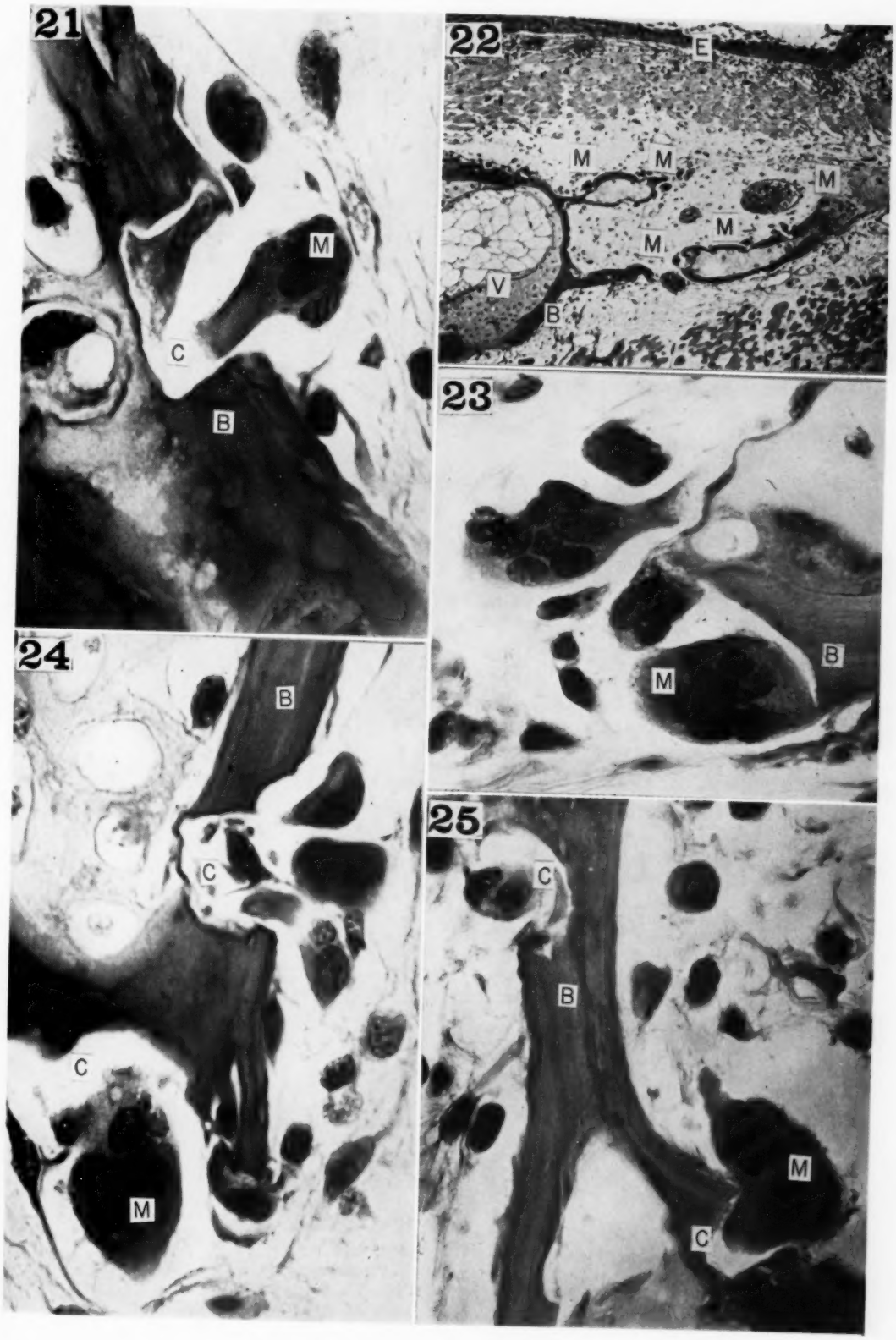
PLATE V.

FIG. 21–25. Portions of longitudinal sections through the tail of young axolotl (No. P-39) 209 days after local irradiation with 1,000 r. B—bone; C—cavity in the bone; E—skin epithelium; M—giant macrophages; V—vertebral body. Photomicrographs ×35 (FIG. 22), ×500 (FIG. 21, 23, 24, and 25).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ally and in most cases only remnants of the lens were found. The lens membrane, forming many small folds, was the most resistant structure. In some cases, macrophages were found in the body of the seriously damaged lens. Apparently, they partially phagocytized and partially dissolved the lens fibers, resulting in destruction of the lens.

DISCUSSION

The resorption process is the result of the reaction of the nonirradiated body to the irradiated limb. The most typical phenomenon in the tissue undergoing resorption is the presence of macrophages.

Resorption after roentgen irradiation is the result of the activity of the macrophages. The disappearance of the skeleton is the main factor in reduction; soft tissues without skeletal support contract and are destroyed more easily by macrophages. Blood vessel damage is probably also an important factor. During advanced reduction all distal capillaries and small blood vessels are destroyed. As a result, many of the large distal blood vessels are transformed into peripheral sinuses. Resorption apparently occurs in the presence of an abnormal blood supply, which may create conditions favorable for its advance. An abnormal blood supply favors the transportation of macrophages into the limb undergoing resorption and, through formation of large sinuses directly under the skin, favors the reduction of skin epithelium.

The resorption which results from macrophage activity may be the specific reaction of amphibians to local irradiation. Reduction or resorption is observed during normal development in certain amphibians. The resorption of tails at the time of metamorphosis of Anura tadpoles is a classic example of such reduction. But resorption in some degree is observed also in Urodella, *i.e.*, the disappearance of the gills and the transformation of the tail during metamorphosis, when the axolotl is transformed into the adult form, Amblystoma. Bataillon,[2] Duesberg,[20] Aleshin,[1] and others showed that resorption of the tadpole's tail occurs by means of phagocytosis and histolysis. Aleshin[1] found large aggregations of macrophages in the tail of the metamorphosing tadpole and showed that resorption of the tail begins and progresses the same as typical inflammation.

Butler[17,18] observed resorption of the cartilaginous skeleton of irradiated regen-

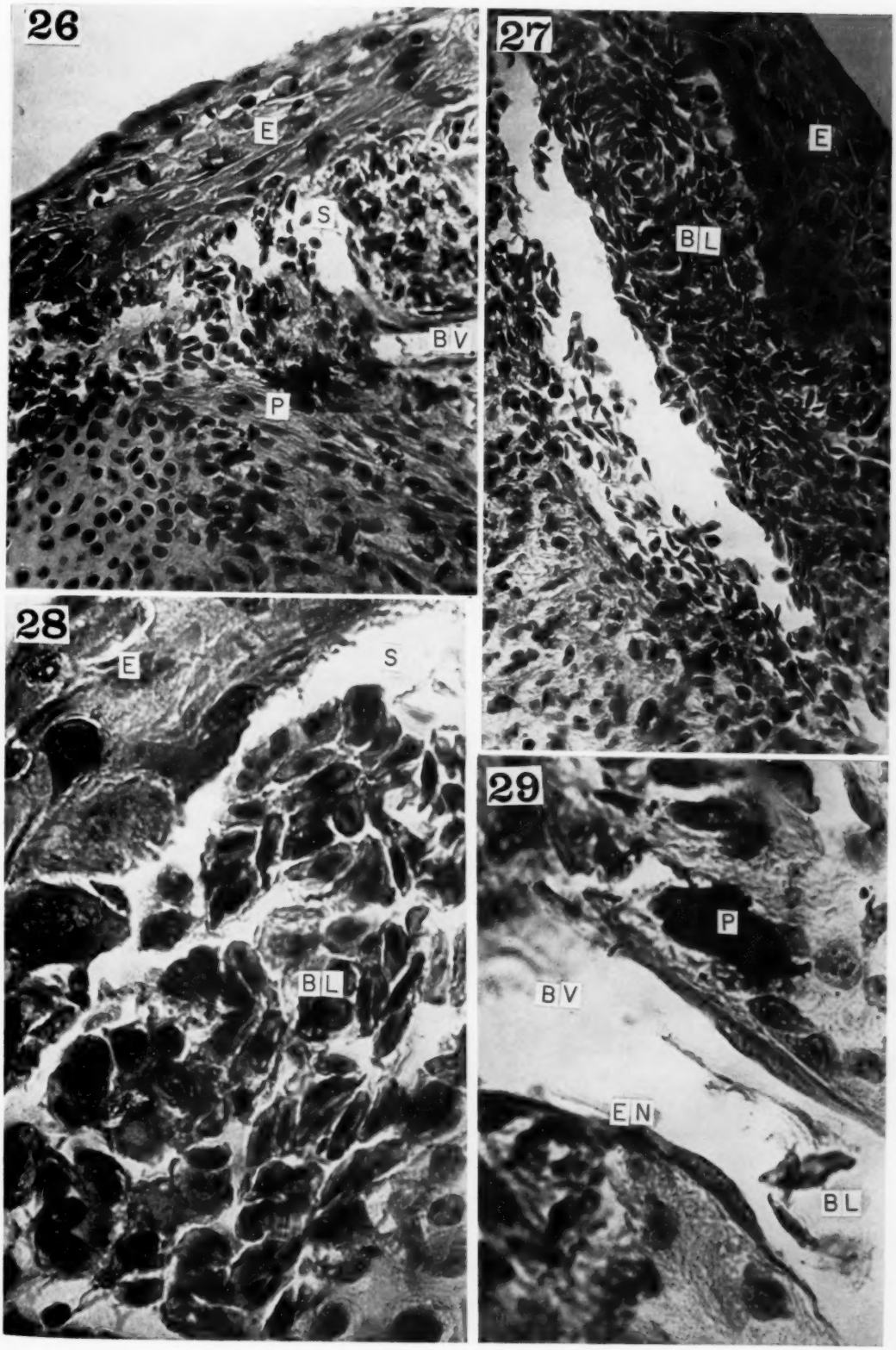
PLATE VI.

FIG. 26. Limb regenerate of axolotl (No. 28) 126 days after local irradiation with 4,000 r. BV—large blood vessel transformed into subepithelial sinus (S); E—skin epithelium; P—pigment cell. Photomicrograph ×150.

FIG. 27. Limb regenerate of axolotl (No. 20) 62 days after local irradiation with 4,000 r. BL—accumulation of blood corpuscles in sinus under skin epithelium (E). Blood vessel walls are absent. Photomicrograph ×150.

FIG. 28. The same specimen as that in Figure 27, under higher magnification. Photomicrograph ×500.

FIG. 29. The same specimen as that in Figures 27 and 28, showing normal endothelial cells (EN) of the blood vessel (BV) from a more proximal region of the limb. P—pigment cell. Photomicrograph ×500.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eration buds in larval stages of Amblystoma punctatum. This disintegration of the cartilaginous skeleton proceeds in a proximal direction. Puckett[21,22] also observed resorption of tissues after irradiation of Amblystoma larvae. Puckett described "giant" cells which were observed during resorption, but did not ascribe any particular significance to them. In spite of the fact that these authors give a completely different interpretation of their findings and suggest a hypothesis of excessive differentiation, they undoubtedly observed the same phenomenon of roentgen regression.

The process of reduction in amphibians is not caused by roentgen treatment alone. For example, regenerating limbs in triton are resorbed following destruction of their innervation.[3,22] Also, the denervated nonregenerating limbs of Amblystoma punctatum, Amblystoma opacum, and Triturus viridescens are resorbed.[18,23]

We conclude that regression or resorption is the specific reaction of amphibians to roentgen radiation or certain other factors and is related to the ability of these animals to undergo transformation during metamorphosis.

SUMMARY

1. Reduction was observed in 90 per cent of the regenerated limbs of adult axolotls irradiated with 4,000 r, and in 100 per cent of those irradiated with 6,000 r. Reduction begins in the distal end and progresses proximally. The skin epithelium is gradually reduced in area without the formation of open wounds.

2. Histologic investigation showed that the conditions of the skin epithelium depended upon the interval between irradiation and fixation. In most cases, early fixation (40–80 days after irradiation) revealed epithelial damage, *i.e.*, formation of giant cell degenerating epithelium, while late fixation (100–128 days after irradiation) revealed normal epithelium. The condition of the epithelium is the result of a specific reaction of this tissue and is independent of the reduction of the limb in general. The mechanism of the epithelium reduction is obscure, but it is independent of macrophage activity. A hypothetical explanation is given. Damage of the subcutaneous pigment layer or separate pigment cells was observed in all cases, but the condition of these cells varied greatly in different areas of the limb.

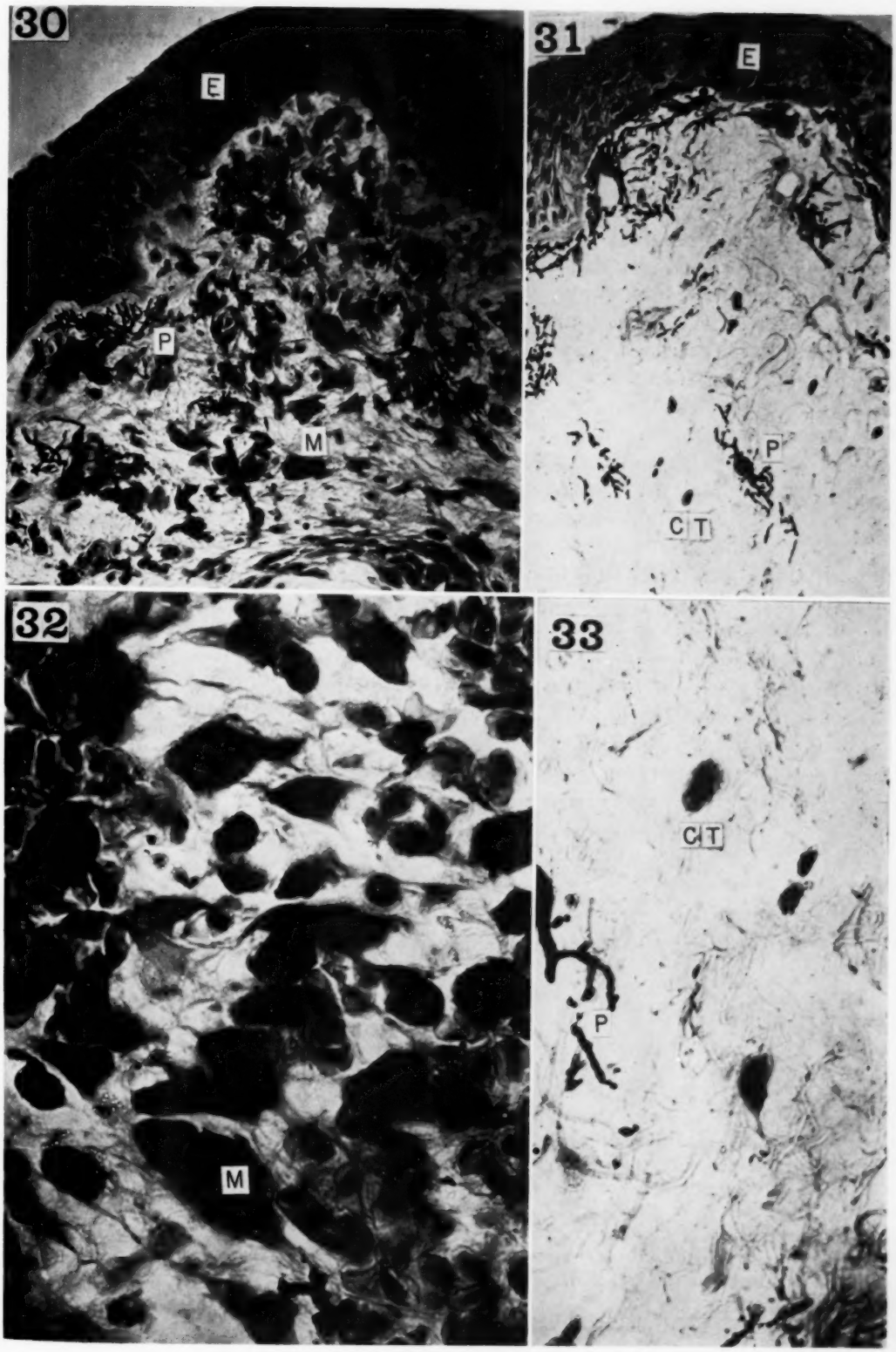
PLATE VII.

FIG. 30. Limb regenerate of axolotl (No. 16) 126 days after local irradiation with 4,000 r. E—skin epithelium, normal in appearance; M—macrophages in loose connective tissue; P—pigment cell. Photomicrograph ×150.

FIG. 31. Limb regenerate of the same animal as that in Figure 30, showing a more proximal, probably nonirradiated, region. CT—cells of loose connective tissue; E—epithelium, normal in appearance; P—pigment cell. Photomicrograph ×50.

FIG. 32. Part of the section through the limb regenerate of axolotl (No. 15) 63 days after local irradiation with 4,000 r, showing an accumulation of macrophages (M) in loose connective tissue. Photomicrograph ×500.

FIG. 33. Limb regenerate of the same animal as that in Figure 31. CT—cells of loose connective tissue; P—pigment cell. Photomicrograph ×500.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3. Resorption of the cartilaginous and bony skeleton is a result of macrophage activity. The attack of macrophages on the skeletal elements always begins at the surface. Bone and cartilage are dissolved as a result of the action of lytic enzymes secreted by macrophages which are located near the skeletal surface. Comparatively small macrophages penetrate deeply into the cartilaginous substance and dissolve the cartilage, forming many empty spaces in various areas. Such spaces are never observed in normal cartilage.

4. During advanced reduction all distal capillaries and small blood vessels disappear and in many cases the large blood vessels in the distal regions are transformed into peripheral sinuses. Resorption occurs in the presence of abnormal blood supply.

5. The loose connective tissue has an important role in the distribution and spread of macrophages. Through this tissue the macrophages can penetrate into the bone, cartilage, and other tissues. During the resorption, the amount of connective tissue is decreased greatly, probably as a result of macrophage activity.

6. During reduction, compact muscle bundles are reduced to isolated small, thin bundles or even isolated, irregularly oriented fibrils and isolated nuclei. Macrophages are found between them. Resorption of muscles is a result of macrophage activity.

7. Resorption of teeth of young and adult axolotls, once it has begun, is completed quickly within 10–15 days and is the result of macrophage activity.

8. Resorption of the lens of the young axolotl after irradiation of the head is the result of macrophage activity.

9. Regression, reduction, or resorption is the result of reaction of the nonirradiated body to the irradiated portion, and is the direct result of macrophage activity.

10. Resorption is a specific reaction of amphibians and is observed during normal development at the time of metamorphosis.

11. Resorption can be provoked by roentgen rays or other factors. This re-

PLATE VIII.

FIG. 34. Limb regenerate of a control animal, showing normal muscle tissue. N—nuclei. Photomicrograph ×150.

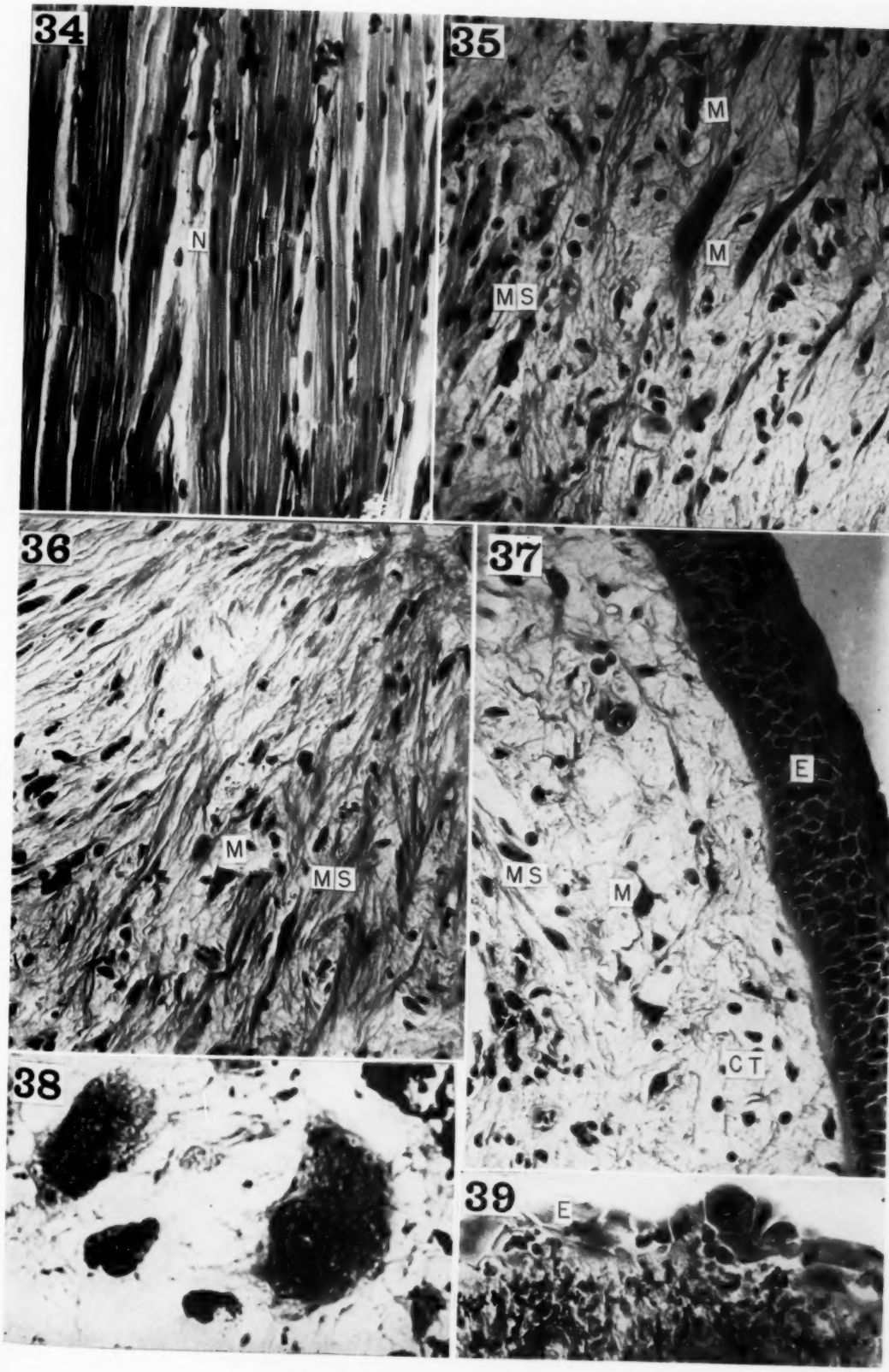
FIG. 35. Limb regenerate of axolotl (No. 28) 126 days after local irradiation with 4,000 r, showing reduction of muscle tissue. M—giant macrophages; MS—muscle nuclei. Photomicrograph ×150.

FIG. 36. Part of the section through the limb regenerate of axolotl (No. 13) 126 days after local irradiation with 4,000 r, showing early stage of muscle reduction. M—macrophages; MS—muscle nuclei. Photomicrograph ×150.

FIG. 37. Limb regenerate of axolotl (No. 28) 126 days after local irradiation with 4,000 r. CT—connective tissue cells; E—skin epithelium; M—macrophage; MS—muscle nuclei. Photomicrograph ×150.

FIG. 38. Limb regenerate of axolotl (No. 13) 126 days after irradiation with 4,000 r, showing giant macrophages. Photomicrograph ×500.

FIG. 39. Limb regenerate of axolotl (No. 17) 63 days after irradiation with 4,000 r. E—giant cell abnormal skin epithelium, consisting of one layer of cells. Photomicrograph ×150.


34
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CT
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sponse is related to the ability of these animals to undergo transformation during metamorphosis.

Roswell Park Memorial Institute
Buffalo 3, New York

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PLATE IX.

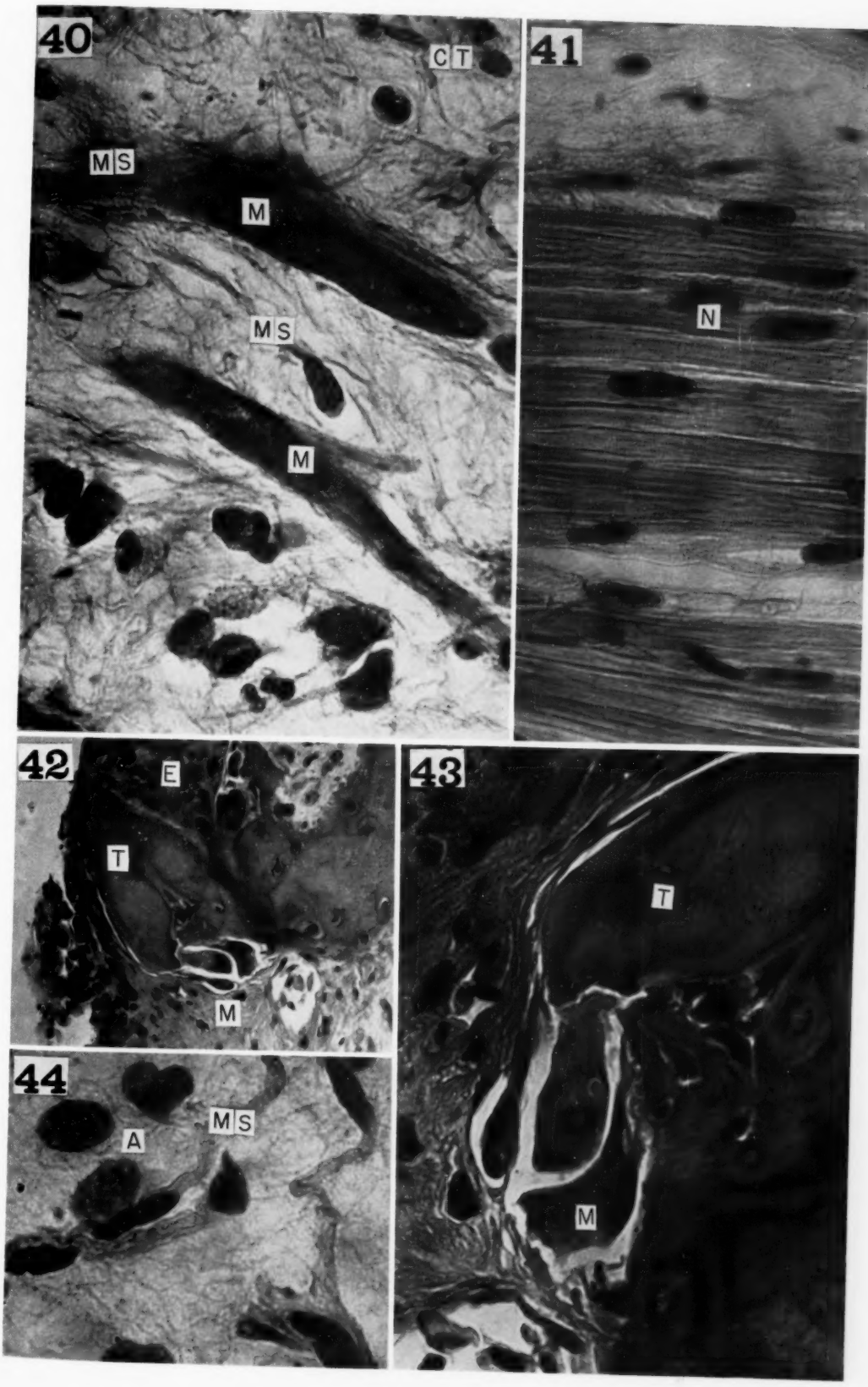
FIG. 40. Limb regenerate of axolotl (No. 28) 126 days after local irradiation with 4,000 r. CT—connective tissue cells; M—giant macrophages; MS—remnants of muscle fibers. Photomicrograph ×500.

FIG. 41. Limb regenerate of control animal. Normal muscle tissue. N—nuclei. Photomicrograph ×500.

FIG. 42. Sagittal section through the jaw of an adult axolotl (No. 17) 144 days after irradiation with 6,000 r. E—oral epithelium; M—macrophages; T—tooth. Photomicrograph ×150. (Reproduced with permission from the *Journal of Dental Research*, 1959, *38*, 301.)

FIG. 43. The same section as that in Figure 42 under higher magnification. Photomicrograph ×500. (Reproduced with permission from the *Journal of Dental Research*, 1959, *38*, 301.)

FIG. 44. Limb regenerate of axolotl (No. 17) 63 days after irradiation with 4,000 r. A—abnormal connective tissue cells; MS—muscle fiber. Photomicrograph ×500.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Vol. 85, No. 1

THE RESPONSE OF SWINE AFTER EXPOSURE TO THE GAMMA-NEUTRON FLUX OF A NUCLEAR DETONATION*

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ALTHOUGH the responses of large mammals exposed to acute whole-body gamma irradiation from a nuclear detonation,[1,13,14] from cobalt 60 gamma rays,[6,10] 1 mv. peak[16] and 2 mv. peak[12] roentgen rays have been well documented, the effects of mixed gamma and neutron radiations from a nuclear detonation have not been reported. Swine, which have a cross sectional diameter similar to that of man, are of particular interest as experimental animals since comparable distributions of depth doses are obtained. The present study was performed during the summer of 1957 (Operation Plumbbob) at the Nevada Test Site to evaluate the responses of swine after exposure to a wide range of prompt radiation doses from a nuclear detonation with a gamma-neutron dose ratio of 1.2. The range of exposure doses obtained was from 410 to 2,475 rads, which afforded a unique opportunity to compare various levels of effect on a population of large mammals. Parameters investigated were physical signs of illness, acute lethality through 45 days, and median survival times.

METHODS

The swine were a Hampshire-Landrace strain with occasional swine having Duroc coloration. They were obtained from a midwest breeder and shipped by double-decked truck to the exposure site. The animals were free from disease and external parasites and were immunized against hog cholera and swine erysipelas. The animals were fed a 14 per cent protein ration and had not received antibiotics in their feed except at weaning (third week). Water was available ad libitum.

Two hundred and sixty-four animals (47 per cent male castrates—53 per cent females) were selected for uniformity of weight (83±11 pounds) and assigned to exposure groups by a system of random numbers.

The animals were exposed in aluminum cylinders (wall thickness ¼ inch) anchored to the ground by cables and stout metal pegs (Fig. 1). Two pigs were placed in each cylinder and 12 animals were exposed at each dose level. After exposure the animals were checked for external radioactive contamination and placed in pens, 24 per pen. Observations were made at frequent intervals thereafter.

Neutron measurements were made in air using threshold detectors of activation foils and fission foils.[3] The foils used and the neutron energy ranges measured directly by activation or by the difference between fission thresholds were:

Foil	*Neutron Energy Range*
Sulfur	Greater than 2.5 mev.
Uranium minus sulfur	1.5 mev. to 2.5 mev.
Neptunium minus uranium	750 kev. to 1.5 mev.
Plutonium minus neptunium	4 kev. to 750 kev.

Neutron fluxes at all energy bands measured decreased exponentially with distance from the detonation; however, the proportion of neutrons in the various energy

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Fig. 1. Aluminum exposure cylinders for swine anchored in place in exposure area.

ranges was unchanged over the distances at which swine were exposed. From the neutron flux measurements, neutron doses were obtained in rads from single collision theory using the following conversion values[4] for each neutron energy range of exposure:

Neutron Energy	*Flux per 1 rad*
Greater than 2.5 mev.	2.5×10^{8} n/cm^2
1.5 mev. to 2.5 mev.	3.2×10^{8} n/cm^2.
750 kev. to 1.5 mev.	4×10^{8} n/cm^2.
4 kev. to 750 kev.	1×10^{9} n/cm^2.

The gamma-neutron dose ratio changed by about eight per cent over the range of animal exposures due to the shorter mean free path of neutrons as compared to gamma rays. The average neutron contribution to the total (gamma plus neutron) rad dose delivered was:

Neutron Energy	*Per Cent Neutron Contribution to Total Exposure Dose*
Greater than 2.5 mev.	10
1.5 mev. to 2.5 mev.	8
750 kev. to 1.5 mev.	13
4 kev. to 750 kev.	14

Gamma ray and neutron measurements were made in air using chlorinated hydrocarbon dosimeter systems. The characteristics of the gamma sensitive (hexylresorcinol stabilized, tetrachloroethylene) and gamma plus neutron sensitive (trichloroethylene overlayed with a water soluble indicator) chemical dosimeters have been reported in detail.[8,9] The dosimeter vials were contained in lithium lined aluminum cans (Fig. 2) to eliminate thermal neutron response of the system. Acidimetric color changes were determined spectrophotometrically and gamma and neutron doses are expressed in rads.

RESULTS

RADIATION RESPONSES IN SWINE

At the time of recovery (about one hour) one animal (1,160 rad group) was found dead as a result of a fractured cervical vertebra. The remaining animals appeared in good condition and there was no evidence that vomiting had occurred in any group. A few swine vomited shortly thereafter during the return trip to the pen area. On arrival at the pen area all swine appeared to eat and drink normally.

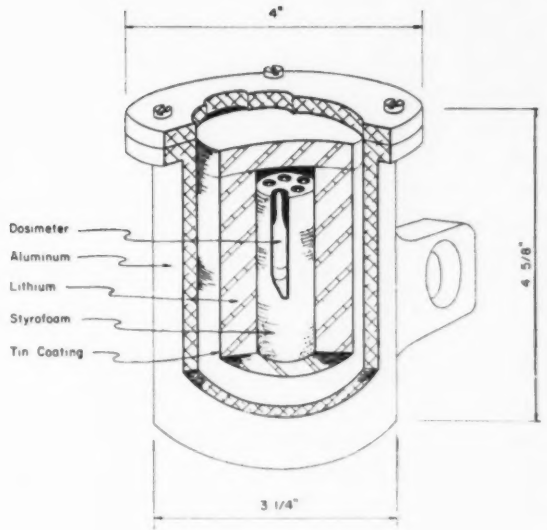

FIG. 2. Schematic drawing and components of chemical dosimeter with aluminum protective can, lithium insert, and glass vials containing organic chemical detector.

The manifestations of acute radiation disease in swine showed three rather distinct phases after gamma-neutron exposure. In general, as the dose was increased, the onset of each phase was more rapid and signs more pronounced.

1. Responses Associated with Exposures from 1,730 to 2,475 rads. Late on the first day after irradiation the swine showed a moderate reduction in volitional activity. At the twenty-four hour feeding there was little food intake and by thirty-six hours intake was nil. All animals in this dose range were vomiting within forty-eight hours and the frequency and severity increased with time. Extreme polydipsia followed by copious vomiting was common. The onset of diarrhea also occurred about forty-eight hours after exposure and consistency rapidly changed from soft stools to a copious watery discharge. Although polydipsia and vomiting subsided late in the third day, diarrhea persisted in most swine until death. Irritability and hyperesthesia were evident late in the second day and most pronounced on the third day. After irritability and hyperesthesia subsided late in the third day the swine were listless and severely ill. Rectal temperatures in some swine rose to 106–109°F. In keep-

ing with the gaunt appearance of the animals was the measured decrease in body weight.

The mode of death varied in this range of exposure doses. Many swine died quietly in deep coma, whereas others had repeated episodes of convulsive activity for several hours prior to death. Death occurred in 106–112 hours. This was similar to the stable 3.5 to 4 day or "gastrointestinal" death seen in rodents after roentgen- and gamma-ray exposures from 1,200 to 10,000 r.

2. Responses Associated with Exposures from 575 to 1,535 rads. Anorexia and vomiting occurred later than for the previous group and their incidence, severity and duration were not marked in the early stages. Vomiting became severe later at the higher doses, with some swine vomiting gross blood. Most of these swine had a transient return of appetite between the fifth and seventh days post irradiation, yet became gaunt and emaciated with a rough hair coat prior to death.

The onset of diarrhea occurred on the fourth and fifth days post exposure. In many swine bloody stools were noted by the end of the first week. Blood clots and gross blood were passed with considerable straining in some animals, while others bled freely while lying down.

By the seventh day bloody froth and bright red blood exuded from the nostrils in many swine. The onset of cutaneous petechiae and/or purpura was noted from the eighth to the twelfth day, appearing on the ventral surface of the abdomen or the medial surfaces of the appendages. These areas developed a livid appearance as the hemorrhagic lesions coalesced. A similar lividity was seen in the ears in the terminal stages of the illness. Frequently swine in this group survived three or four days after the onset of bleeding. Edema of the appendages and rarely of the snout, not seen at higher doses, appeared from the seventh to the twelfth day.

Gross and ophthalmoscopic observations revealed only extreme congestion of the sclerae throughout the illness.

3. Responses Associated with Exposures from 410 to 515 rads. The syndrome associated with median lethal doses was characterized by a transient loss of appetite and vomiting and diarrhea which occurred about the third day. This was followed by a period of apparent normal health and continued weight gain until the appearance of the hemorrhagic syndrome at 8 to 10 days following exposure. Hemorrhagic signs were more pronounced in those animals which eventually succumbed, yet which lived sufficiently long for manifestations of granulocytopenia and thrombocytopenia to develop fully. Bleeding from body orifices, elevated temperature, and ataxia were significantly more frequent in decedents. Death usually occurred on the fourteenth or fifteenth day and this phase of radiation sickness has been described in detail for a variety of experimental animals.

LETHALITY

Listed in Table 1 are the percentages of deaths at 30 days for swine exposed to graded doses of gamma rays and neutrons. When per cent mortality was plotted against dose, a sigmoid response curve was obtained. Probit transformation of the data using the method described by Finney[2] gave a regression line of the type.

$$Y = a + bx$$

where Y was the probit of per cent mortality and x was log radiation dose in rads. Figure 3 shows the relationship of per cent mortality for varying doses of gamma plus neutron irradiation. Median lethal doses at various times after exposure are listed in Table II. The LD_{50} at 45 days was not altered from the 30 day value by the death of the one animal at the forty-second day post exposure.

MEDIAN SURVIVAL TIME

Median survival time at each dose level was determined by plotting probit of per cent survival against the logarithm of time from exposure. The best line of fit was

TABLE I

MORTALITY AND SURVIVAL TIMES OF SWINE AFTER GAMMA-NEUTRON IRRADIATION

Exposure Dose (rads)	Days after Irradiation																			Lethality (per cent)	Median Survival Time (hr.)
	1	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	42		
2,475		1	10	1																100	106
2,185		1	11																	100	107
1,935		2	6	4																100	112
1,730		3	6	3																100	109
1,535			3	7	1	1														100	125
1,325			2	7	3															100	134
1,300			3	5	2	1		1												100	137
1,205		1	1	5	1	3	1													100	139
1,160	1*			6	3	2														100	143
1,070			1	3	2	3	3													100	156
1,030			2	2	4	2	2													100	147
955				1	2	2	1	1	2	2				1						100	210
915					5	2	4			1										100	180
845					3	5	3		1											100	178
820					2	5	2	2											1	100	182†
760				1	2	3	1			2						1				83.3	182
730					1	2	1	5	1			2								100	218
645								1	2	4	3		1	1						100	273
575						1	1		3	2			1	1		1				83.3	270
515									1		1		2	1		1		1		58.3	350
455											1			1		1	1			33.3	360
410													1	1						16.7	360

* Animal dead on recovery, not included in lethality or survival time results.
† Not including animal dying on forty-second day.

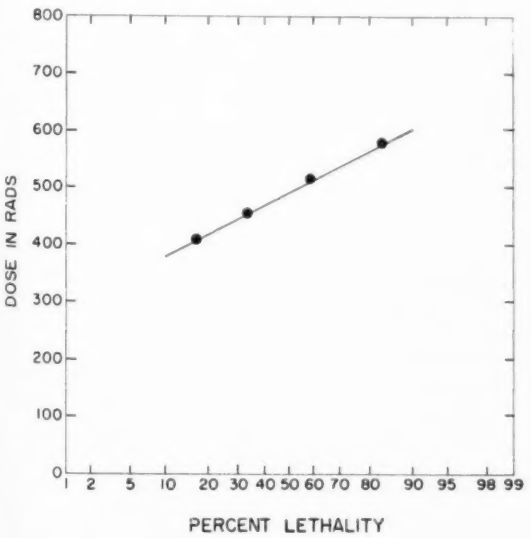

FIG. 3. Thirty-day lethality in swine as a function of dose of gamma-neutron irradiation from a nuclear detonation.

drawn through the data, and the point corresponding to a probit 5 or 50 per cent survival was taken as the median survival time. Survival times are listed in Table 1.

DISCUSSION

The physical signs of acute sickness in swine exposed to a wide range of gamma-

TABLE II

MEDIAN LETHAL DOSE AT VARIOUS TIMES AFTER EXPOSURE

Time after Exposure (da.)	Median Lethal Dose (rads)
5	1,570 (1,439–1,714)
10	711 (662– 764)
15	565 (514– 621)
30–45	486 (478– 496)

neutron doses from a nuclear detonation have been described. Although fission neutrons contributed about 45 per cent of the total dose delivered, there was little difference in the incidence, severity, and duration of acute radiation sickness in swine as compared to roentgen or gamma irradiation.[1,10,11,13,14,15]

Podalgia and abnormal gait were observed as reported in swine after cobalt 60 irradiation[10] and may be associated with hemorrhage into joint spaces as observed in this study and as reported elsewhere.[14] Ocular lesions reported after low dose rate exposures to cobalt 60 gamma rays[10] were not observed however.

The LD_{50} value of 486 rads at 30 days is in good agreement with values reported for swine and other large mammals after roentgen or gamma irradiation.[6,12,13,16] Considering the variations in biologic response and differences in exposure factors reflected in the $LD_{50/30}$ values obtained, the differences were, indeed, not large. The previously reported value of 230 r for swine exposed to gamma rays from a nuclear device[13] was significantly lower. In the present study neither gamma rays nor fission neutrons were obtained as discrete radiations. However, if an effectiveness of 1 is assigned to gamma rays and if the effect of gamma plus neutron irradiation is assumed to be additive, the relative effectiveness of fission neutrons is then about 1.2 (the gamma-neutron dose ratio) for the production of lethality.

The survival times of swine were similar to those seen in rodents and monkeys over the same range of doses; however, quantitative differences appeared to exist between swine and the other species. The median survival time for swine irradiated with doses of about the median lethal range was 14–15 days as compared to the 10–11 day death time of rodents. The dose dependent region of survival response occurred in swine after doses from 575 to 1,535 rads. A stable plateau in survival time of 4–5 days appeared to have been reached for the swine at somewhat higher total doses than for the $3\frac{1}{2}$ day gastrointestinal death in rodents and monkeys. Since no group of swine had a median survival time less than 4–5 days, the threshold for "central nervous system death" was not exceeded and has been reported in excess of 2,475 rads.[7]

SUMMARY

1. The responsiveness of 264 swine exposed to doses from 410 to 2,475 rads of gamma-neutron radiation from a nuclear dentonation has been described.

2. The LD_{50} value at 30 days was 486 (478–496) rads.

3. Median survival times for swine were similar to those of other mammalian species.

4. The potency of fission neutrons as compared to gamma rays from a nuclear detonation was estimated to be about 1.2 for the production of lethality at 30 days in swine.

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The success of a radiation effects study of this nature, conducted under field conditions, is obviously contingent upon a variety of circumstances such as weather, source strength, and the close cooperation of a rather heterogenous group of scientific personnel. In large part these results are the efforts of the splendid group of noncommissioned officers and enlisted personnel assigned to the project.

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* *Ex officio.*

EDITORIAL

MULTIPLE MYELOMA AND INTRAVENOUS PYELOGRAPHY

IN 1933, Bell[1] advanced the theory that the excretion of Bence Jones proteins in the urine of patients afflicted with multiple myeloma leads to laminated deposits of hyaline casts in the renal tubules, exerting gradual mechanical obstruction followed by glomerular atrophy and chronic progressive uremia. Oliver[2] in 1945, through a series of morphologic demonstrations, supported this "stopped pipes" theory and he has shown that the deposition of laminated Bence Jones protein casts may occur in the entire nephron up to the proximal convoluted tubules. This concentric laminated appearance of the casts, together with the sequential changes resulting from the gradual obstruction produced by them, is so characteristic that at autopsy it often permits the establishment of a diagnosis of multiple myeloma from a study of the kidney alone. Consequently, the term of "myeloma kidney" was coined to express this pathognomonic significance. It must be mentioned, however, that paramyloidosis, secondary hypogammaglobulinemia and some alternative modes of Bence Jones protein damage may also play a role in producing the renal insufficiency. The presence of some kidney changes has been observed in 48–90 per cent of multiple myeloma patients in several series reported and uremia was found to be, after pneumonia, the most frequent cause of death.

Very recently Sanchez and Domz[3] gave an excellent account of the clinical manifestations which may be attributed to these kidney changes. They categorized the renal syndromes associated with multiple myeloma into: acute glomerulonephritis, nephrotic syndrome, water-losing nephritis, adult Fanconi's syndrome, renal tubular acidosis, acute tubular necrosis, and acute and chronic pyelonephritis. The most important observation made by Sanchez and Domz, however, is the fact that "renal disease is a common guise under which myeloma may masquerade and elude diagnosis" before other more tangible signs become apparent. This elusiveness was also noted by Osserman,[4] who in 2 cases fortuitously discovered dysproteinemia during the course of study for unrelated conditions and was able to establish the diagnosis of multiple myeloma before skeletal changes could be demonstrated roentgenographically. In one patient, who died with signs of hypercalcemia and renal functional impairment, both the documented asymptomatic and symptomatic periods were extremely brief. In the second patient skeletal changes developed one year after the discovery of the abnormal protein. The difficulty of diagnosis in occult multiple myeloma is further complicated by the additional facts that (a) at times extramedullary involvement of organs other than the kidney, as for example of the lung, pleura, retroperitoneal lymph nodes or testicle, may constitute the principal feature of the disease and (b) a 5 per cent incidence of the Bence Jones proteinuria or dysproteinemia is observed in such conditions as malignant lymphomas, metastatic tumors of bone, idiopathic hemolytic disease, the "essen-

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tial" cryoglobulinemia and very rarely in a few other lesions.

The proper evaluation of myeloma kidney and associated or related lesions is of considerable interest to the radiologist since recent evidence is accumulating which shows that it is hazardous to perform intravenous pyelography in patients afflicted with such lesions. In cases with frank multiple myeloma, precise assay of the renal involvement is usually not difficult and the danger thus can easily be avoided. However, in the occult cases and especially in those in which the renal disease is not even suspected as reflecting the main clinical feature of a possible myelomatous process, the use of intravenous pyelography may prove disastrous.

Bartels, Brun, Gammeltoft and Gjørup[5] were the first to make this observation in 1954. They performed intravenous pyelography in a male, aged sixty-nine, who complained of fatigue and flank pain; he had increased blood urea nitrogen and proteinuria, but no Bence Jones protein. The patient, who was suspected of having myelomatosis, developed "acute" anuria following the intravenous pyelography and died forty days later. At postmortem examination casts were found extensively filling the tubules. In 1956, Myhre, Brodwall and Knutsen[6] reported 2 similar cases. One patient, a male aged seventy, died eleven days after intravenous pyelography. The other, a male aged forty-two, recovered from the acute episode but died in uremia eight months later. At postmortem examination cast-plugged tubules were the outstanding finding. In 1957, Kielmann, Gjørup and Thaysen[7] reported the case of a male, aged thirty-six, with multiple myeloma, who had marked proteinuria with demonstration of abnormal proteins. This patient went into acute renal failure immediately after the intravenous pyelography and died nine days later. At postmortem examination only a few casts were found in the tubules.

In 1958, Perillie and Conn[8] analyzed in detail the various aspects of the above mentioned cases and reported an additional case of their own. In this case, a male thirty-four years old, proteinuria and hyperglobulinemia were present and roentgenograms revealed general osteoporosis with small multiple osteolytic lesions of the vertebral bodies and ribs. Plasma cell myeloma was suspected. Intravenous pyelography was performed which showed normal excretion of the contrast medium and normal structures. Nausea and vomiting developed on the day after pyelography and the subsequent course was one of progressive renal failure complicated by recurrent epistaxes, nausea, and vomiting. He died in uremia almost three months after pyelography. Postmortem examination revealed that the tubules which were markedly dilated were filled, particularly in the proximal portions, with inspissated casts in varying stages of formation. Perillie and Conn also mention another case of plasma cell myeloma, personally communicated to them by Walsh, in which anuria was induced by intravenous pyelography resulting in the death of the patient.

Sanchez and Domz[3] report a case of occult multiple myeloma in which the dominant clinical picture was hypertensive azotemia and intravenous pyelography was performed in the hope of uncovering a correctable renal lesion. The patient died with congestive heart failure and postmortem examination disclosed multiple myeloma, with generalized arteriolar paramyloidosis, particularly severe in the kidney. It is the opinion of Sanchez and Domz that hypertensive, instead of the usual normotensive, azotemia may occur in multiple myeloma in

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the presence of paramyloidosis or as a result of renal ischemia and may completely overshadow the basic disease, as in their own case. They also state that in retrospect the attempt at intravenous pyelography appears to have been unwise. They believe that multiple myeloma may be present sometimes for years in an occult form, detectable only when searched for, and that if such patients have renal involvement disaster may be precipitated with "disconcerting swiftness" after minor stress.

The well known survey of 1955 by Pendergrass, Hodes, Tondreau, Powell and Burdick[9] on the deaths and unfavorable sequelae following the administration of contrast media in urography encompasses more than 3,800,000 urographic examinations over an eleven year period. There were 25 immediate deaths which were attributed to allergic reactions. In addition, there were 3 delayed deaths which occurred one, two and three days, respectively, following intravenous pyelography. All 3 of these patients had increased blood urea nitrogen and died in uremia. Since the clinical findings were not available and no mention was made of a postmortem examination, it is difficult to say whether intravenous pyelography had any role in inducing the uremia but the possibility cannot be excluded.

Perillie and Conn,[8] in discussing the mechanism of acute renal failure which occurred in the 5 cases reviewed by them, believe that precipitation of intratubular proteins is the main factor and they postulate that intravenous pyelography may set the stage for this precipitation in the following way. Cleansing cathartics and enemas preparatory to examination produce dehydration which is considerably increased by fasting and withdrawal of fluids. Dunbar, MacEwan and Hebert,[10] in a comprehensive study performed on normal male adults and experimentally in rabbits, recently demonstrated that there is a slight and consistent improvement in the quality of the intravenous pyelograms following dehydration, due to increased urinary concentration. Abdominal compression to block the flow of the contrast containing urine reduces renal blood flow and thereby further increases the urinary concentration, thus enhancing the precipitation of the abnormal proteins within the tubules. The plugging of the lower nephron then swiftly leads to obstructive uropathy, with oliguria, anuria and death.

Although the cited cases may appear unusual and may represent rare instances in the large number of intravenous pyelographic examinations performed routinely, certain precautions are definitely warranted. These are: Intravenous pyelography should not be performed in frank cases of multiple myeloma for any reason. In the occult cases of multiple myeloma, a diligent search should be made for protein abnormalities by electrophoretic studies of the blood serum and urine and, if their presence is demonstrated, intravenous pyelography should be omitted. In the cases of proteinuria of undetermined cause, the possibility of a multiple myeloma "masquerading" under the guise of a nephropathy should be kept in mind and intravenous pyelography performed only after the elimination of this possibility.

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NATIONAL COMMITTEE ON RADIATION PROTECTION AND MEASUREMENTS

A NUMBER of actions and activities of the NCRP and its subcommittees seem to be worthy of note at this time.

Just recently two new organizations have been accepted as sponsors. These are the American Nuclear Society and the Genetics Society of America. The NCRP is very happy, indeed, to have these two organizations assist in its programs.

Another action taken recently involved the reactivation of Subcommittee 1. This subcommittee under the chairmanship of H. H. Parker met on October 18, 1960 and began an active program, reflecting its concern with the development of the basic concepts and philosophy of radiation protection. The subcommittee decided to operate under a pattern that has been found to be successful with other subcommittees. It will have a small working group assisted by an advisory group or consultants as circumstances demand. The initial membership includes: H. M. Parker, Chairman, R. H. Chamberlain, J. F. Crow, H. Curtis, H. F. Friedell, H. J. Muller, C. Powell, H. H. Rossi.

Subcommittee 14 on "Permissible Exposure Doses under Emergency Conditions" under the chairmanship of G. V. LeRoy has been very active of late. A report of the subcommittee directed particularly to the problems of civil defense officials is now nearing completion and is expected to be submitted to the NCRP Main Committee in the near future.

Subcommittee M-4 on "Relative Biological Effectiveness" now under the chairmanship of V. P. Bond has also begun a very active program. They have outlined a method of approach for their program and begun preliminary work on a report. Arrangements have been made for liaison between this subcommittee and the joint ICRU-ICRP group concerned with similar problems.

Two new handbooks have been released during recent months and a number of others are now nearing completion. Handbook 72 on "Measurement of Neutron Flux and Spectra for Physical and Biological Applications" was released on July 15, 1960. Handbook 73 on "Protection Against Radiations from Sealed Gamma Sources" was released on July 27, 1960. Handbook 75 on "Measurement of Absorbed Dose of Neutrons and Mixtures of Neutrons and Gamma Rays" and Handbook 76, "Medical X-rays Protection up to Three Million Volts" (Revision of Handbook 60), are now at the printers and should be released soon. Two other handbooks are now undergoing editorial review and it is hoped that they, too, can soon be released. These are: "Stopping Powers for Use with Cavity Chambers" and "A Manual of Radioactivity Procedures."

REPORT OF THE INTERNATIONAL COMMISSION ON RADIOLOGICAL UNITS AND MEASUREMENTS

COMMITTEE ON THE METHODS OF RADIOLOGICAL EQUIPMENT AND MATERIALS

Subcommittee on Focal Spots

METHOD OF FOCAL SPOT IMAGE AND MEASUREMENT

(For Diagnostic Tubes Up to 150 Kev)

AT THE 1956 meetings of the International Commission on Radiological Units and Measurements, a new committee was established to study methods of evaluating radiological equipment and materials; it operates under the Chairmanship of Dr. B. Combee of the Netherlands with Dr. E. D. Trout of the U.S.A. as Vice-Chairman. A series of subcommittees have been set up to deal with specialized subjects. The report to follow is the first of the subcommittee reports to be completed.

As problems of radiation units and measurements have developed during recent years it has become increasingly evident that it is not feasible for the ICRU to publish a regular triennial report covering all areas of interest to the Commission. Therefore, it has been decided that as different committees or subcommittees of the Commission complete their reports they will be released for whatever journal publication may appear to be appropriate. Approximately every three years the committee will endeavor to compile as many of these reports as possible into a single report. By this procedure it is hoped to avoid holding up the release of one completed study, simply to have it included in a single report with all other studies.

This report of Subcommittee IV of the ICRU is the first such report to be released in the manner described above. It will also be included as Appendix II in the triennial report of the ICRU due for publication within a few months.

Committee IV of the ICRU consists of the following members: B. Combee, Chairman, Netherlands; E. Dale Trout (Vice Chairman), U.S.A.; E. Zieler (Technical Secretary), Germany; H. Berger, Germany; Bernard O'Loughlin, U.S.A.; A. S. Johnstone, England; J. Massiot, France; D. J. Stevens, Australia; S. W. Smith, U.S.A.; C. W. Wegelius, Sweden.

The Subcommittee (IV-1) that prepared this specific report consists of the following members: T. Rogers (Chairman), U.S.A.; G. M. Ardran, England; E. Fenner, Germany; R. Griffoul, France; A. Kuntke, Germany.

This report has been reviewed and approved by the ICRU.

Lauriston S. Taylor, Chairman

METHOD OF FOCAL SPOT IMAGE AND MEASUREMENT

Introduction

Report of the International Commission on Radiological Units and Measurements Subcommittee IV-1 on Focal Spots

The task of this Subcommittee has been considerably simplified by the instruction given to it in the report of ICRU IV dated August 14, 1958, as follows:

"Only the tools for making an accurate measurement under any desired operating conditions should be specified. The specification of tolerances allowable from nominal focal sizes, of the tube current and voltage conditions should be considered to be outside the scope of ICRU IV."

Consistent with this instruction, the Subcommittee has given special attention to methods of measurement of focal spot size in X-ray tubes for diagnosis. In this report we submit our recommendations for a measurement method and procedure suitable for such tubes, particularly of the line

focus variety, when operated at voltages not exceeding 150 kvp.

At the ICRU meeting held in Geneva, September, 1958, it was suggested that Subcommittee I should also include in its task the method of measurement of uniformity of focal spots and that the studies should not be limited to diagnostic tubes but should include therapy tubes and possibly radioactive sources. The Subcommittee has not as yet been able to evaluate this suggestion. It is of the opinion, however, that a method applicable specifically for diagnostic tubes can and should be recommended at this time, and that therapy tubes and radioactive sources should be the subject of further deliberation.

The following recommendations represent a composite of the positions taken by the individual members of the Subcommittee with respect to the various points involved rather than the unanimous opinion of all. However, a majority are in agreement that the method proposed will give a substantially accurate measure of the effective focal size of an X-ray tube under the operating conditions obtained at the time the measurement is made.

RECOMMENDATIONS

METHOD OF FOCAL SPOT IMAGE FORMATION AND MEASUREMENT

(For diagnostic tubes at voltages up to 150 kvp.)

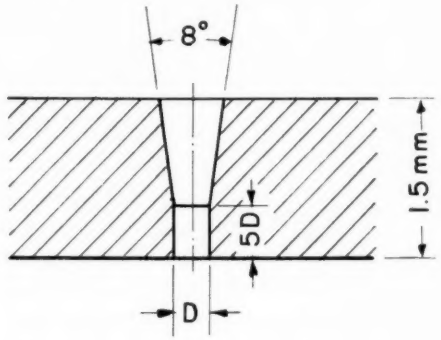
1. *Basic method*

Pinhole radiograph of focal spot, produced by pinhole accurately aligned with respect to "central ray" of X-ray beam.

2. *Details of pinhole camera*

a. Pinhole diameter: .030 mm. for focal sizes below 1.0 mm.; .075 mm. for focal sizes 1.0 mm. to 2.5 mm.; .100 mm. for focal sizes above 2.5 mm.

b. Diaphragm thickness, material, and pinhole profile: The pinhole diaphragm shall be manufactured from a 90/10 gold-platinum alloy, 1.5 mm. thick. The cylindrical part of the pinhole shall be five times as long as its diameter and followed by a conical part with a divergent angle of 8° (see diagram below).



c. Focal spot to pinhole distance: 10 cm. minimum (where focus location is not precisely known or directly measurable, precise location stereoscopically with dual pinholes is recommended).

d. Enlargement factor: 2.0 minimum for focal sizes up to 2.5 mm.; 1.0 minimum for focal sizes above 2.5 mm.

3. *Photographic technique*

a. Type of film: Any commonly used dental film (single coating).

b. Image density: 0.6 to 1.0, as measured in the most dense portion of the image. Density to be controlled by means of standard developing technique and proper exposure time at tube current and voltage factors employed. (This element involves a point of special difficulty, because of variations in structure of respective focal spots. If lines in focal spot are superimposed, greater maximum density results than in cases where lines are not superimposed, for equal exposure values. Hence a wide latitude in allowable maximum density become necessary.)

4. *Measurement of image*

a. Lighting: Back-lighted at approximately 20 foot-candles.

b. Measurement procedure: Use scaled magnifier with 0.1 mm. scale divisions, 5 to 10 times magnification. Measure length and width, respectively, including all perceptible portions of the image, to nearest 0.1 mm. For irregularly shaped (non-

rectangular) focal spots, measurement should be taken of all significant dimensions.

c. Correction of image measurements: All image dimensions shall be divided by the enlargement factor, accurately determined (see 2d).

5. *Statement of dimensions*

a. Width of focal spot shall be stated as the width of the image divided by the enlargement factor.

b. Length of focal spot shall be stated as the length of the image divided by the enlargement factor, further corrected by a multiplier of 0.7.[a]

c. For non-rectangular focal spots, all significant dimensions, including maximum diameter, shall be stated as indicated by actual measurements divided by the enlargement factor.[b]

APPENDIX A

The proposal of a fractional multiplier for correction of the measured image length arises from the long-recognized fact that the lengthwise distribution of energy in the focal spot of a line-focus tube tends to be peaked at the center and diminishes gradually to zero at the ends. Hence, the effective length, based on its effect on either radiographic definition or loading capacity, cannot be stated as equal to the measured image length as initially corrected. Some further correction is necessary. This point has been exposed, and to some extent explored in the papers heretofore presented by Polansky and O'Conner[1] (1954), Rogers[2] (1956), Fenner and Jochim[3] (1957), and Servais,[4] (1958). However, we do not feel that work done to date has been sufficiently comprehensive to establish a suitable correction factor, and the suggestion above of a multiplier of 0.7 is given primarily by way of example or as an approximate value rather than as a final recommendation. We would like to recommend that ICRU IV enlist the good offices of a suitable research organization to explore this matter quantitatively over the entire range of diagnostic tubes commercially produced, with the objective of establishing a proper formula for focal spot length.

[a] See Appendix A for explanation.
[b] See Appendix B for explanation.

APPENDIX B

Off-Focus Radiation

It must be recognized that the effect of any off-focus radiation on definition is not taken into account by these measurements, and unless off-focus radiation is suppressed, the definition to be expected from the tube may be influenced by it.

REFERENCES

1. Polansky, D., and O'Conner, D. T. X-ray focal spot measurement. *Nondestructive Testing*, 1954, *12*, 1.
2. Rogers T. H. Definition and measurement of focal spot size of x-ray tube. Presented at the Eighth International Congress of Radiology, Mexico City, July 24, 1956.
3. Fenner, E., and Jochim, H. Bestimmung der Brennfleckgrösse aus der geometrischen Unschärfe. *Fortschr. a. d. Geb. d. Röntgenstrahlen*, 1957, *87*, 109–115.
4. Servais, J. Le contrôle des foyers d'émission dans les tubes radiogènes et relation entre la largeur du foyer et al netteté relative des images radiographiques. *J. de radiol. et d'électrol.*, 1958, *39*, 383–388.

SOCIETY PROCEEDINGS AND NEWS ITEMS

MEETINGS OF RADIOLOGICAL SOCIETIES*

UNITED STATES OF AMERICA

AMERICAN ROENTGEN RAY SOCIETY
Secretary, Dr. C. Allen Good, Mayo Clinic, Rochester, Minn. Annual meeting: Deauville Hotel, Miami Beach, Fla., Sept. 26–29, 1961.

AMERICAN RADIUM SOCIETY
Secretary, Dr. Charles G. Stetson, 350 Engle Street, Englewood, N. J. Annual meeting: Broadmoor Hotel, Colorado Springs, Colo., May 11–14, 1961.

RADIOLOGICAL SOCIETY OF NORTH AMERICA
Secretary, Maurice Doyle Frazer, 1037 Stuart Bldg., Lincoln, Neb.
Treasurer, Dwight Vincent Needham, 713 E. Genessee St., Syracuse, N. Y. Annual meeting: to be announced.

AMERICAN COLLEGE OF RADIOLOGY
Executive Director, William C. Stronach, 20 N. Wacker Drive, Chicago 6, Illinois. Annual meeting: Chicago, Ill., Feb. 8–11, 1961.

SECTION ON RADIOLOGY, AMERICAN MEDICAL ASSOCIATION
Secretary, Dr. Clyde A. Stevenson, Sacred Heart Hospital, West 101 Eighth Ave., Spokane 4, Wash. Annual meeting: New York City, June 26–30, 1961.

AMERICAN BOARD OF RADIOLOGY
Secretary, Dr. H. Dabney Kerr. Correspondence should be directed to Kahler Hotel Building. Rochester, Minn. The Spring 1961 examination will be held at the Denver Hilton Hotel, Denver, Colorado, June 19–22, inclusive; the deadline for filing applications was January 1, 1961. There will be no Special Examination in Nuclear Medicine. The Fall 1961 examination will be held at the Shoreham Hotel, Washington, D. C., December 4–7, inclusive; the deadline for filing applications is July 1, 1961. A Special Examination in Nuclear Medicine will be offered if there are sufficient applications.

TENTH INTERNATIONAL CONGRESS OF RADIOLOGY
Secretary-General, Dr. Carleton B. Peirce, Royal Victoria Hospital, Montreal 2, Quebec, Canada. Meets in Montreal, Aug. 26–Sept. 1, 1962.

SEVENTH INTER-AMERICAN CONGRESS OF RADIOLOGY
Counselor for the United States, Dr. J. A. del Regato, Penrose Cancer Hospital, 2200 North Cascade Avenue, Colorado Springs, Colorado. The meeting will be held in São Paulo, Brazil, September 3–10, 1961.
Secretary-General, Dr. Walter Bomfim-Pontes, Rua Cesario Motta, No. 112, São Paulo.

ALABAMA RADIOLOGICAL SOCIETY
Secretary, Dr. J. A. Meadows, Jr., Medical Arts Bldg., Birmingham 5, Ala. Meets time and place Alabama State Medical Association.

AMERICAN NUCLEAR SOCIETY
Executive-Secretary, Octave J. Du Temple, 86 E. Randolph St., Chicago, Ill.

ARIZONA RADIOLOGICAL SOCIETY
Secretary, Dr. Don E. Matthieson, 926 East McDowell Rd., Phoenix, Ariz. Two regular meetings a year. Annual meeting at time and place of State Medical Association and interim meeting six months later.

ARKANSAS RADIOLOGICAL SOCIETY
Secretary, Dr. J. B. Scruggs, Arkansas Baptist Hospital, Little Rock, Ark. Meets every three months and also at time and place of State Medical Association.

ASSOCIATION OF UNIVERSITY RADIOLOGISTS
Secretary, Dr. Melvin M. Figley, Department of Radiology, University of Washington, Seattle 5, Wash. Annual meeting to be announced.

ATLANTA RADIOLOGICAL SOCIETY
Secretary, Dr. Wilson T. Edenfield, 35 Linden Ave., N.E., Atlanta 8, Ga. Meets monthly, except during three summer months, on second Friday evening.

BLOCKLY RADIOLOGICAL SOCIETY
Secretary, Dr. Samuel Finkelman, 101 S. Twentieth St. Philadelphia, Pa.

BROOKLYN RADIOLOGICAL SOCIETY
Secretary, Dr. Joseph Arcomano, 168 Clinton St., Brooklyn 1, N. Y. Meets first Thursday of each month October through May.

BUFFALO RADIOLOGICAL SOCIETY
Secretary, Dr. Kenneth H. Seagrave, 537 Delaware Ave., Buffalo 2, N. Y. Meets second Monday evening each month, October to May inclusive.

CENTRAL NEW YORK RADIOLOGICAL SOCIETY
Secretary, Dr. Joseph A. Head, 150 Marshall St., Syracuse, N. Y. Meets first Monday each month October through May.

CENTRAL OHIO RADIOLOGICAL SOCIETY
Secretary, Dr. Robert L. Freidman, Grant Hospital, Columbus, Ohio. Meets at 6:30 P.M. on second Thursday of October, November, January, March and May at Fort Hayes Hotel, Columbus, Ohio.

CENTRAL SOCIETY OF NUCLEAR MEDICINE
Secretary, Dr. Robert S. Landauer, Radiation Center Building, 1903 West Harrison St., Chicago 12, Ill.

CHICAGO ROENTGEN SOCIETY
Secretary, Dr. William F. Hutson, 5145 N. California Ave., Chicago, Ill. Meets second Thursday of each month, October to April except December at the Sheraton Hotel at 8:00 P.M.

CLEVELAND RADIOLOGICAL SOCIETY
Secretary, Dr. Norman E. Berman, 14404 S. Park Blvd., Shaker Hgts. 20, Ohio. Meetings at 7:00 P.M. on fourth Monday of each month from October to April at Tudor Arms Hotel.

COLORADO RADIOLOGICAL SOCIETY
Secretary, Dr. Bertram L. Pear, 3705 East Colfax Ave., Denver 6, Colo. Meets third Friday of each month at Denver Athletic Club from September through May.

CONNECTICUT VALLEY RADIOLOGIC SOCIETY
Secretary, Dr. Paul J. Kingston, 114 Woodland St., Hartford, Conn. Meets first Friday in February and April.

DALLAS-FORT WORTH RADIOLOGICAL CLUB
Secretary, Dr. W. H. Neil, 1217 W. Cannon St., Fort Worth, Texas. Meets monthly, third Monday, at Greater Fort Worth International Airport at 6:30 P.M.

DETROIT ROENTGEN RAY AND RADIUM SOCIETY
Secretary, Dr. Kenneth L. Krabbenhoft, Harper Hospital, Detroit 1, Mich. Meets monthly first Thursday, October through May, at David Whitney House, 1010 Antietam, at 6:30 P.M.

EAST BAY ROENTGEN SOCIETY
Secretary, Dr. Dan Tucker, 434 30th St., Oakland 9, Calif. Meets first Thursday each month at Peralta Hospital, Oakland.

EAST TENNESSEE RADIOLOGICAL SOCIETY
Secretary, Dr. J. Marsh Frere, Jr., 205 Medical Arts Building, Knoxville, Tenn. Meets in January and September.

EASTERN CONFERENCE OF RADIOLOGY
Secretary, Arrangements Committee, Dr. Philip Myers, Baltimore City Hospital, Baltimore 24, Md. Annual meeting: Lord Baltimore Hotel, Baltimore, Md., March 9–11, 1961.

*** Secretaries of societies are requested to send timely information promptly to the Editor.**

Eastern Radiological Society
Secretary, Dr. John D. Osmond, Jr., Euclid-Glenville Hospital, Cleveland 19, Ohio. Meets at Mid Pines Club Southern Pines, N. C., April 16–19, 1961.

Florida Radiological Society
Secretary, Dr. John P. Ferrell, 166 4th Ave., St. Petersburg, Fla. Meets twice annually, in the spring with the annual State Society Meeting, and in the fall.

Florida West Coast Radiological Society
Secretary-Treasurer, Dr. Joseph C. Rush, 1800 Druid Rd., Clearwater, Fla.

Georgia Radiological Society
Secretary, Dr. George W. Brown, Griffin, Ga. Meets in spring and fall with Annual State Society Meeting.

Greater Miami Radiological Society
Secretary, Dr. Donald H. Altman, 2751 Coral Way, Miami, Fla. Meets monthly third Wednesday at 8 P.M. at Jackson Memorial Hospital, Miami, Fla.

Greater St. Louis Radiological Society
Secretary, Dr. Harvey A. Humphrey, 462 N. Taylor, St. Louis 8, Mo.

Houston Radiological Society
Secretary, Dr. Edward B. Singleton, 6621 Fannin St., Houston 25, Texas. Meets last Monday each month, Seminar Room, Doctors' Club of Houston.

Idaho State Radiological Society
Secretary, Dr. Claude W. Barrick, St. Alphonsus Hospital, Boise, Idaho. Meets in the Spring and Fall.

Illinois Radiological Society
Secretary, Dr. George A. Miller, Carle Hospital Clinic, Urbana, Ill. Meets in spring and fall.

Indiana Roentgen Society, Inc.
Secretary, Dr. David E. Wheeler, 1500 North Ritter, Indianapolis, Ind. Meets first Sunday in May and during fall meeting of Indiana State Medical Association.

Iowa Radiological Society
Secretary, Dr. L. L. Maher, 1419 Woodland Ave., Des Moines, Iowa. Luncheon and business meeting during annual session of Iowa State Medical Society. The scientific section is held in the autumn.

Kansas Radiological Society
Secretary, Dr. Lewis G. Allen, 807 Huron Bldg., Kansas City, Kansas. Meets in spring with State Medical Society, and in winter on call.

Kentucky Radiological Society
Secretary, Dr. Robert H. Akers, V. A. Hospital, Louisville 2, Ky. Meets monthly on second Friday at Seelbach Hotel, Louisville.

Kings County Radiological Society
Secretary, Dr. Abraham Berens, 1917 Bedford Ave., Brooklyn 25, N. Y. Meets Kings County Med. Soc. Bldg. monthly on fourth Thursday, October to May, 8:45 P.M.

Los Angelfs Radiological Society
Secretary, Dr. Walter Stilson, 1720 Brooklyn Ave., Los Angeles, Calif. Meets second Wednesday of month in September, November, January, April and June at Los Angeles County Medical Association Building, Los Angeles.

Maine Radiological Society
Secretary, Dr. Albert A. Poulin, Thayer Hospital, Waterville, Maine. Meets in June, September, December and April.

Maryland Radiological Society
Secretary, Dr. Nathan B. Hyman, 1805 Eutaw Place, Baltimore 17, Md.

Memphis Roentgen Society
Secretary, Dr. Hollis H. Halford, Kennedy V.A. Hospital, Department of Radiology, Memphis 15, Tenn. Meets first Monday of each month at John Gaston Hospital.

Miami Valley Radiological Society
Secretary, Dr. S. F. Johnson, 2197 Los Arrow Dr., Dayton 9, Ohio. Meets second Friday of fall and winter months.

Mid-Hudson Radiological Society
Secretary, Dr. Joseph Sorrentino, St. Francis Hospital, Poughkeepsie, N. Y. Meets 8:30 P.M., fourth Wednesday each month, September to May.

Milwaukee Roentgen Ray Society
Secretary, Dr. Joseph F. Wepfer, 5000 W. Chambers St., Milwaukee 10, Wis. Meets monthly on fourth Monday, October through May, at University Club.

Minnesota Radiological Society
Secretary, Dr. Donald H. Peterson, 853 Medical Arts Bldg., Minneapolis 2, Minn. Meets three times annually, in fall, winter and spring.

Mississippi Radiological Society
Secretary, Dr. Bernard T. Hickman, University Medical Center, Jackson, Miss. Meets third Thursday of each month at Hotel Edwards, Jackson, at 6:00 P.M.

Montana Radiological Society
Secretary, Dr. J. K. Boughn, 35 11th Ave., Helena, Montana. Meets at least once a year.

Nassau Radiological Society
Secretary, Dr. Alan E. Baum, 100 Nowbridge Rd., Hicksville, N. Y. Meets second Tuesday of the month in February, April, June, October and December.

Nebraska Radiological Society
Secretary, Dr. Ronald E. Waggener, The Radiologic Center, Nebraska Methodist Hospital, Omaha 31, Nebraska. Meets third Wednesday of each month at 6 P.M. in Omaha or Lincoln.

New England Roentgen Ray Society
Secretary, Dr. Robert E. Wise, 605 Commonwealth Ave., Boston 15, Mass. Meets third Friday of each month, October through May at The Longwood Towers, Brookline, Mass.

New Hampshire Roentgen Ray Society
Secretary, Dr. Paul Y. Hasserjian, 1470 Elm St., Manchester, N. H. Meets four to six times yearly.

New York Roentgen Society
Secretary, Dr. Albert A. Dunn, 622 W. 168th St., New York, N. Y. Meets monthly on third Monday, New York Academy of Medicine at 4:30 P.M.

North Carolina Radiological Society
Secretary, Dr. A. B. Croom, 624 Quaker Lane, High Point, N. C. Meets in the spring and fall each year.

North Dakota Radiological Society
Secretary, Dr. R. F. Raasch, Post Office Box 990, Dickinson, North Dakota. Meets at time of State Medical Association meeting. Other meetings arranged on call of the President.

North Florida Radiological Society
Secretary, Dr. Paul A. Mori, 800 Miami Road, Jacksonville 7, Fla. Meets quarterly in March, June, September and December.

Northeastern New York Radiological Society
Secretary, Dr. Lester I. Citrin, St. Mary's Hospital, Troy, N. Y. Meets in Albany area on second Wednesday of October, November, March and April.

Northern California Radiological Society
Secretary, Dr. Rob H. Kirkpatrick, 1219 28th St., Sacramento, Calif. Meets at dinner last Monday of each month, September to June.

Ohio State Radiological Society
Secretary, Dr. Paul D. Meyer, 125 S. Grant Ave., Columbus, Ohio. Annual meeting third week end in May, 1961 at Columbus, Ohio.

Oklahoma State Radiological Society
Secretary, Dr. E. D Greenberger, Medical Arts Bldg., McAlester, Okla. Meets in January, May and October.

Oregon Radiological Society
Secretary, Dr. George R. Satterwhite, 1123 S.W. Yamhill, Portland, Ore. Meets monthly from October to June on the second Wednesday of each month at 8:00 P.M. at the University Club.

Orleans Parish Radiological Society
Secretary, Dr. Joseph V. Schlosser, Charity Hospital, New Orleans 13, La. Meets second Tuesday of each month.

Pacific Northwest Radiological Society
Secretary, Dr. John N. Burkey, 555 Dental Bldg., Seattle, Wash. Annual meeting: Portland, Oregon, May, 1961.

Pacific Roentgen Society
Secretary, Dr. L. H. Garland, 450 Sutter St., San Francisco 8, Calif. Meets annually during meeting of California Medical Association.

Pennsylvania Radiological Society
Secretary, Dr. Frederick R. Gilmore, 234 State St., Harrisburg, Pa. Annual meeting: Bedford Springs Hotel, May 26–27, 1961.

Philadelphia Roentgen Ray Society
Secretary, Dr. Robert B. Funch, Department of Radiology, Germantown Hospital, Philadelphia 44, Pa. Meets first Thursday of each month, at 5 P.M., from October to May in Thompson Hall, College of Physicians.

Pittsburgh Roentgen Society
Secretary, Dr. Ross H. Smith, St. Margaret Memorial Hospital, Forty-Sixth St., Pittsburgh 1, Pa. Meets second Wednesday of month, October through June at Park Schenely Restaurant.

Radiological Section, Baltimore Medical Society
Secretary, Dr. James K. V. Willson, 1100 N. Charles St., Baltimore 1, Md. Meets third Tuesday each month, September to May, inclusive.

Radiological Society of Greater Cincinnati
Secretary, Dr. Donald Janny, Cincinnati, Ohio. Meets monthly from September to May on first Monday of each month at 7:30 P.M. at the Cincinnati General Hospital.

Radiological Society of Hawaii
Secretary, Dr. Philip S. Arthur, 274 Young Hotel Bldg., Honolulu, Hawaii. Meets third Monday of each month at 7:30 P.M.

Radiological Society of Greater Kansas City
Secretary, Dr. J. Stewart Whitmore, 1010 Rialto Bldg., Kansas City, Mo. Meets last Friday of each month.

Radiological Society of Kansas City
Secretary, Dr. Arthur B. Smith, 800 Argyle Bldg., Kansas City, Mo. Meets third Thursday of each month.

Radiological Society of Louisiana
Secretary, Dr. Robyn Hardy, 4324 Magnolia St., New Orleans 15, La. Meets annually during Louisiana State Medical Society meeting.

Radiological Society of New Jersey
Secretary, Dr. Austin J. Tidaback, 912 Prospect Ave., Plainfield, N. J. Meets at Atlantic City at time of State Medical Society meeting and in November in Newark, N. J.

Radiological Society of New York State
Secretary-Treasurer, Dr Mario C. Gian, 610 Niagara St., Buffalo 1, N. Y. Annual meeting to be announced.

Radiological Society of South Dakota
Secretary-Treasurer, Dr. Donald J. Peik, 303 S. Minnesota Ave., Sioux Falls, S. D.

Radiological Society of Southern California
Secretary, Dr. Joseph F. Linsman, 436 N. Roxbury Dr., Beverly Hills, Calif.

Redwood Empire Radiological Society
Secretary, Dr. Lee E. Titus, 164 W. Napa St., Sonoma, Calif. Meets second Monday every other month.

Richmond County Radiological Society
Secretary, Dr. W. F. Hamilton, Jr., University Hospital, Augusta, Ga. Meets first Thursday of each month at various hospitals.

Rochester Roentgen Ray Society, Rochester, N. Y.
Secretary, Dr. Robert H Greenlaw, 188 Irvington Rd., Rochester 20, N. Y. Meets at 8:15 P.M. on the last Monday of each month, September through May, at Strong Memorial Hospital.

Rocky Mountain Radiological Society
Secretary, Dr. John H. Freed, 4200 East Ninth Ave., Denver 20, Colo. Annual meeting: Denver Hilton Hotel, Denver, Colo., Aug. 10–12, 1961.

San Antonio-Military Radiological Society
Secretary, Dr. Hugo F. Elmendorf, Jr., 730 Medical Arts Bldg., San Antonio 5, Texas. Meets third Wednesday each month in Fort Sam Houston Officer's Club at 6:30 P.M.

San Diego Radiological Society
Secretary, Dr. Stanley A. Moore, 2466 First Ave., San Diego 1, Calif. Meets first Wednesday of each month at the University Club.

San Francisco Radiological Society
Secretary, Dr. M. A. Sisson, 450 Sutter St., San Francisco 8, Calif. Meets quarterly at the San Francisco Medical Society, 250 Masonic Ave., San Francisco 18, Calif.

Section on Radiology, California Medical Association
Secretary, Dr. William H. Graham, 630 East Santa Clara St., San Jose, Calif.

Section on Radiology, Connecticut State Medical Society
Secretary, Dr. Wayne P. Whitcomb, Hospital of St. Raphael, New Haven, Conn. Meetings are held bimonthly.

Section on Radiology, Medical Society of the District of Columbia
Secretary, Dr. William E. Sheely, 1746 K St., N.W., Washington 6, D. C. Meets at Medical Society Library, third Wednesday of January, March, May and October at 8:00 P.M.

Section on Radiology, Illinois State Medical Society
Secretary, Dr. William Meszaros, 1825 W. Harrison St., Chicago, Ill.

Section on Radiology, Southern Medical Association.
Secretary. Dr. Seymour Ochsner, Ochsner Clinic, 3503 Prytania St., New Orleans 15, La. Annual meeting to be announced.

Shreveport Radiological Club
Secretary, W. R. Harwell, 608 Travis St., Shreveport, La. Meets monthly on third Wednesday, at 7:30 P.M., September to May inclusive.

Society for Pediatric Radiology
Secretary, Dr. Richard G. Lester, 412 Union St., S.E., Minneapolis 14, Minn. Annual meeting: Deaville Hotel, Miami Beach, Fla., Sept. 25, 1961.

Society of Nuclear Medicine
Secretary, Dr. Robert W. Lackey, 452 Metropolitan Bldg., Denver 2, Colo. *Administrator*, Samuel N. Turiel, 430 N. Michigan Ave., Chicago 11, Ill. Annual meeting: Penn Sheraton Hotel, Pittsburgh, Pa., June 14–17, 1961.

South Bay Radiological Society
Secretary, Dr. Stanford B. Rossiter, 1111 University Dr., Menlo Park, Calif. Meets second Wednesday of each month.

South Carolina Radiological Society
Secretary, Dr. George W. Brunson, 1406 Gregg St., Columbia, S. C. Annual meeting (primarily business) in conjunction with the South Carolina Medical Association meeting in May. Annual fall scientific meeting at time and place designated by the president.

Southern Radiological Conference
Secretary, Dr. Marshall Eskridge, Mobile Infirmary, Mobile, Ala.

Southwestern Radiological Society
Secretary, Dr. Ralph S. Clayton, 1501 Arizona, Bldg. 2-A, El Paso, Texas. Meets second Tuesday of each month.

Tennessee Radiological Society
Secretary, Dr. James J. Range, P.O. Box 324, Johnson City, Tenn. Meets annually at the time and place of the Tennessee State Medical Association meeting.

Texas Radiological Society
Secretary, Dr. R. P. O'Bannon, 402 Professional Bldg., 1216 Pennsylvania Ave., Fort Worth 4, Texas. Next meeting January 20 and 21, 1961, Texas Hotel, Fort Worth, Texas.

Tri-State Radiological Society
Secretary, Dr. James R. Mathews, 118 S. E. First St., Evansville, Ind. Meets last Wednesday of Oct., Jan., March and May, 8:00 P.M. at Elks' Club in Evansville.

University of Michigan Department of Roentgenology Staff Meeting
Meets each Monday evening from September to June, at 7:00 P.M. at University Hospital.

Upper Peninsula Radiological Society
Secretary, Dr. A. Gonty, Menominee, Mich. Meets quarterly.

Utah State Radiological Society
Secretary, Dr. Richard Y. Card, St. Mark's Hospital, Salt Lake City, Utah. Meets fourth Wednesday in January, March, May, September and November at Holy Cross Hospital.

Virginia Radiological Society
Secretary, Dr. Frank A. Kearney, II, 110 S. Curry St., Phoebus, Va. Meets annually in October.

Washington State Radiological Society
Secretary, Dr. Joseph T. Houk, 14303 Ambaum Blvd., Seattle 66, Wash. Meets third Monday of each month from September through April at the University of Washington Medical School.

West Virginia Radiological Society
Secretary, Dr. Karl J. Myers, 112 N. Woods St., Philippi, W. Va. Meets concurrently with Annual Meeting of West Virginia State Medical Society; other meetings arranged by program committee.

Westchester Radiological Society
Secretary, Dr. Richard P. Avondu, Yonkers General Hospital, Park & Ashburton Ave., Yonkers, N. Y. Meets on third Tuesday of January and October and on two other dates.

Wisconsin Radiological Society
Secretary, Dr. Howard G. Bayley, 116 Iroquois Parkway, Beaver Dam, Wis. Annual meeting each spring in various places.

X-Ray Study Club of San Francisco
Secretary, Dr. John H. Heald, 450 Sutter St., San Francisco 8, Calif. Meets monthly, third Thursday at 7:30 P.M., Children's Hospital, September through June.

Cuba, Mexico, Puerto Rico and Central America

Asociación de Radiólogos de Centro America y Panamá. Comprising: Guatemala, El Salvador, Honduras, Nicaragua, Costa Rica and Panamá.
Secretary-General, Dr. Julio Toriello, 11 Calle 2-37, zona 1, Guatemala. Meets annually in a rotating manner in the six countries.

Sociedad de Radiología de El Salvador
Secretary, Dr. Rafael Vega Gómez.

Sociedad de Radiología de Guatemala
Secretary, Dr. Carlos E. Escobar, 9ª. Calle A 0-05, Zona 1, Guatemala.

Sociedad de Radiología y Fisioterapía Cubana
Secretary, Dr. Miguel A. García Plasencia, Hospital Curie, 29 y F, Vedado, Habana, Cuba. Meets monthly at Curie Hospital.

Sociedad Costarricense de Radiologia
Secretary, Dr. James Fernández Carballo, Apartado VIII, San José, Costa Rica.

Sociedad Mexicana de Radiología, A. C.
Calle del Oro No. 15, México 7, D. F
Secretary-General, Dr. E. Alvarez Hernández. Meets first Monday of each month.

Asociación Puertorriqueña de Radiología
Secretary, Dr. R. B. Díaz Bonnet, Suite 504, Professional Bldg., Santurce, Puerto Rico.

Sociedad Radiológica Panameña
Secretary, Dr. L. Arrieta Sánchez, Apartado No. 6323, Panamá, R. de P. Meets monthly in a department of radiology of a local hospital, chosen at preceding meeting.

British Commonwealth of Nations

Association of Radiologists of the Province of Quebec
Secretary, Dr. Odilon Raymond, 5400 Blvd. Gouin. Quest, Montreal, Que. Meets four times a year.

British Institute of Radiology Incorporated with the Röntgen Society
Honorary Secretary, Dr. John Blewett, 32 Welbeck St., London, W. 1. Meets monthly from October until May.

Faculty of Radiologists
Honorary Secretary, Dr. R. A. Kemp Harper, 47 Lincoln's Inn Fields, London, W.C.2, England. Annual meeting to be announced.

Section of Radiology of the Royal Society of Medicine ((Confined to Medical Members),
Meets third Friday each month at 4:45 P.M. at the Royal Society of Medicine, 1 Wimpole St., London, W. 1.

Canadian Association of Radiologists
Honorary Secretary, Dr. Robert G. Fraser, *Associate Honorary Secretary*, Dr. Jean-Louis Léger, 1555 Summerhill Ave., Montreal 25, Que. Annual meeting: January 22–25, 1961, Saint John, New Brunswick.

Montreal Radiological Study Club
Secretary, Dr. F. McConnell, 1650 Cedar Ave., Montreal, Quebec. Meets first Tuesday evening, October to April.

Section of Radiology, Canadian Medical Association
Secretary, Dr. C. M. Jones, Inglis St., Ext. Halifax, N. S.

Société Canadienne-Française d'Electro-Radiologie Médicale
General Secretary, Dr. Louis Ivan Vallée, 1058 rue St-Denis, Montreal 18, Canada. Meets third Saturday each month.

Toronto Radiological Society
Secretary, Dr. L. R. Harnick, Toronto Western Hospital, 399 Bathurst St., Toronto, Ontario. Meets second Monday of each month September through May.

College of Radiologists of Australasia
Honorary Secretary, Dr. E. A. Booth, c/o British Medical Agency, 135 Macquarie St., Sydney, N.S.W., Australia.

South America

Asociación Argentina de Radiología
Secretary, Dr. Lidio G. Mosca, Avda. Gral. Paz 151, Córdoba, Argentina. Meetings held monthly.

Ateneo de Radiologia
Secretary, Dr. Victor A. Añaños, Instituto de Radiologia, Santa Fe 3100, Rosario, Argentina. Meets monthly on second and fourth Fridays at 7:00 P.M. in the Hospital Nacional del Centenario, Santa Fe 1300, Rosario.

Colégio Brasileiro de Radiologia
Secretary-General, D. Camillo Segreto, Avenida Angélica, 1.170, Caixa Postal 5984, São, Paulo, Brazil.

Sociedad Argentina de Radiología, Junta Central Buenos Aires
Secretary, Dr. Edgardo O. Olcese, Santa Fé 1171, Buenos Aires. Meetings are held monthly.

Sociedad Bolivana de Radiología
Secretary, Dr. Javier Prada Méndez, Casilla 1596, La Paz, Bolivia. Meets monthly. General assembly once every two years.

Sociedade Brasileira de Radiologia
Secretary, Dr. Nicola Caminha, Av. Mem. de Sa, Rio de Janeiro, Brazil. General Assembly meets every two years in December.

Sociedade Brasileira de Radioterapia
Secretary, Dr. Oscar Rocha von Pfuhl, Av. Brigadeiro Luiz Antonio, 644 São Paulo, Brazil. Meets monthly on second Wednesday at 9:00 P.M. in São Paulo at Av. Brigadeiro Luiz Antonio, 644.

Sociedad Chilena de Radiología
Secretary, Dr. J. P. Velasco, Avenida Santa María 0410, Santiago, Chile. Meets fourth Friday of each month.

SOCIEDAD COLOMBIANA DE RADIOLOGIA
Secretary, Dr. Alberto Mejía Diazgranados, Carrera 13, No. 25–31, Apartado aéreo No. 5804, Bogotá, Colombia. Meets last Thursday of each month.

SOCIEDAD ECUATORIANA DE RADIOLOGÍA Y FISIOTERAPÍA
Secretary, Dr. Publio Vargas P., Casilla 1242, Guayaquil, Ecuador.

SOCIEDAD PARAGUAYA DE RADIOLOGÍA
Secretary, Dr. Miguel González Addone, 15 de Agosto 322, Asunción, Paraguay.

SOCIEDAD PERUANA DE RADIOLOGIA
Secretary, Dr. Luis Pinillos Ganoza, Apartado 2306, Lima, Perú. Meets monthly except during January, February and March, at Asociación Médica Peruana "Daniel A. Carrión," Villalta 218, Lima.

SOCIEDAD DE RADIOLOGIA DEL ATLANTICO
Secretary, Dr. Raul Fernandez, Calle 40 #41-110, Baranquilla, Colombia. Society meets monthly at the Instituto de Radiologia.

SOCIEDAD DE RADIOLOGÍA, CANCEROLOGÍA Y FÍSICA MÉDICA DEL URUGUAY
Secretary-General, Dr. Ernesto H. Cibils, Av. Agraciada 1464, piso 13, Montevideo, Uruguay.

SOCIEDADE DE RADIOLOGIA DE PERNAMBUCO
Secretary, Dr. Manoel Medeiros, Instituto de Radiologia da Faculdade de Medicina da Universidade do Recife, Caixa Postal 505, Pernambuco, Brazil.

SOCIEDAD DE ROENTGENOLOGIA Y MEDICINA NUCLEAR DE LA PROVINCIA DE CÓRDOBA
Secretary-General, Dr. Carlos A. Oulton, Santa Rosa 447, Córdoba, Argentina.

SOCIEDAD VENEZOLANA DE RADIOLOGÍA
Secretary-General, Dr. Rubén Merenfeld, Apartado No. 9362, Candelaria, Caracas, Venezuela. Meets monthly third Friday at Colegio Médico del Distrito Federal, Caracas.

CONTINENTAL EUROPE

ÖSTERREICHISCHE RÖNTGEN-GESELLSCHAFT
President, Dr. Konrad Weiss, Mariannengasse 10, Vienna 9, Austria. Meets second Tuesday of each month in Allgemeine Poliklinik.

SOCIÉTÉ BELGE DE RADIOLOGIE
General Secretary, Dr. S. Masy, 256 Chaussée de Wavre, Heverlee-lez-Louvain, Belgium. Meets in February, March, May, June, October, November and December.

SOCIÉTÉ FRANÇAISE D'ELECTRORADIOLOGIE MÉDICALE, and its branches: SOCIÉTÉ DU SUD-OUEST, DU LITTORAL MÉDITERRANÉEN, DU CENTRE ET DU LYONNAIS, DU NORD, DE L'OUEST, DE L'EST, ET D'ALGER ET D'AFRIQUE DU NORD. Central Society meets third Monday of each month, except during July, August and September, rue de Seine 12, Paris.
Secretary-General, Dr. Ch. Proux, 9, rue Daru, Paris 8e, France.

ČESKOSLOVENSKÁ SPOLEČNOST PRO ROENTGENOLOGII A RADIOLOGII
Secretary, Dr. Robert Poch, Praha 12, Šrobárova 50, Czechoslovakia. Meets monthly except during July, August, and September. Annual general meeting.

DEUTSCHE RÖNTGENGESELLSCHAFT
Secretary, Professor Dr. med. H. Lossen, Universitäts-Röntgeninstitut. Lagenbeckstr. 1, Mainz, Germany. Annual meeting: April 12–15, 1961.

SOCIETÀ ITALIANA DI RADIOLOGIA MEDICA E DI MEDICINA NUCLEARE
Secretary, Dr. Ettore Conte, Ospedale Mauriziano, Torino, Italy. Meets annually.

NEDERLANDSE VERENIGING VOOR ELECTROLOGIE EN RÖNTGENOLOGIE
Secretary, Dr. J. R. von Ronnen, Violenweg 14, den Haag Netherlands.

SCANDINAVIAN ROENTGEN SOCIETIES
The Scandinavian roentgen societies have formed a joint association called the Northern Association for Medical Radiology, meeting every second year in the different countries belonging to the Association.

SOCIEDAD ESPAÑOLA DE RADIOLOGÍA Y ELECTROLOGÍA MÉDICAS Y MEDICINA NUCLEAR
Secretary, Dr. D. Aureo Gutierrez Churruca, Esparteros, No. 9, Madrid, Spain. Meets monthly in Madrid.

SCHWEIZERISCHE GESELLSCHAFT FÜR RADIOLOGIE UND NUKLEARMEDIZIN (SOCIÉTÉ SUISSE DE RADIOLOGIE ET DE MÉDECINE NUCLÉAIRE)
Secretary, Dr. Max Hopf, Effingerstrasse 47, Bern, Switzerland.

INDIA

INDIAN RADIOLOGICAL ASSOCIATION
Secretary, Dr. R. F. Sethna, Navsari Building, Hornby Road, Bombay 1, India.

The next list of Meetings of Radiological Societies will be published in the March, 1961 issue of the JOURNAL.

THIRTEENTH ANNUAL MIDWINTER RADIOLOGICAL CONFERENCE

The Thirteenth Annual Midwinter Radiological Conference, sponsored by the Los Angeles Radiological Society, will be held at the Biltmore Hotel, Los Angeles, California, on Saturday and Sunday, January 28 and 29, 1961.

An outstanding program of pertinent interest has been arranged and the guest speakers will be Dr. James W. D. Bull, London, England; Dr. John Boland, New York, New York; Dr. John A. Kirkpatrick, Philadelphia, Pennsylvania; and Dr. John F. Holt, Ann Arbor, Michigan.

The conference fee of $20.00 includes two luncheon meetings featuring questions and answers. A banquet ($7.50 per plate) preceded by cocktails will be held Saturday evening. Reservations may be made through: Joseph Parks, M.D., 14500 Sherman Circle, Van Nuys, California.

Courtesy cards will be available to residents in Radiology and Radiologists in the Armed Forces by advance registration, with reduced rates for the luncheons and banquet. Hotel reservations should be made promptly through the Convention Manager, Biltmore Hotel, Los Angeles, Calif.

EASTERN CONFERENCE OF RADIOLOGY

The annual meeting of the Eastern Conference of Radiology will be held March 9–11, 1961, at the Lord Baltimore Hotel, Baltimore, Maryland. The Secretary of the Arrangements Committee is Dr. Philip Myers, Baltimore City Hospital, Baltimore 24, Maryland.

COURSE IN CLINICAL USE OF RADIOACTIVE ISOTOPES

A course in the clinical use of radioactive isotopes will be given under the supervision of Dr. Sergei Feitelberg and Dr. Edith Quimby of the Department of Radiology, Columbia University, New York City, from June 5 through June 30, 1961. This is a full-time course which includes lectures, experimental laboratory exercises, clinical rounds and clinical measurements on patients and on specimens. In addition to Drs. Feitelberg and Quimby, the teaching staff will comprise sixteen invited lecturers from the New York area, each presenting material in his own special field.

Enrollment in the class is limited to 20; the fee is $300.

Inquiries should be addressed to Dr. Sergei Feitelberg, Mt. Sinai Hospital, Fifth Avenue at 100th Street, New York, N.Y.

COURSE IN RADIOLOGY AND RADIOACTIVE ISOTOPES

A three-day postgraduate course in Radiology and Radioactive Isotopes has been announced for February 20, 21, and 22, 1961 at the University of Kansas Medical Center, Kansas City, Kansas. A guest faculty of eight nationally recognized authorities will present didactic material.

Information concerning the program and registration may be had by writing the Department of Postgraduate Medical Education, The University of Kansas School of Medicine, Kansas City 12, Kansas.

NEW OFFICERS OF THE RADIOLOGICAL SOCIETY OF NORTH AMERICA

At the Forty-sixth Annual Meeting of the Radiological Society of North America held at the Netherland Plaza Hotel, Cincinnati, Ohio, December 4–9, 1960, the following officers were elected: President, M. Milton Berg, Bismarck, North Dakota; President-Elect, Charles McCurdy Gray, Tampa, Florida; First Vice President, Philip J. Hodes, Philadelphia, Pennsylvania; Second Vice President, John R. Hodgson, Rochester, Minnesota; Third Vice President, George Cooper, Jr., Charlottesville, Virginia; New Member of Board of Directors, John William Walker, Kansas City, Missouri; Secretary, Maurice Doyle Frazer, Lincoln, Nebraska; Treasurer, Dwight Vincent Needham, Syracuse, New York; and Historian, Howard P. Doub, Detroit, Michigan.

Drs. Thomas Burke Bond, Fort Worth, Texas and Warren H. Cole, Chicago, Illinois, were awarded the Gold Medal, highest honor of the Society. Dr. Howard P. Doub was presented with a beautiful silver platter "in appreciation of twenty years of loyal service as Editor of *Radiology*."

BOOKS RECEIVED

COMPARATIVE EFFECTS OF RADIATION; Report of a Conference held in San Juan at the University of Puerto Rico, February 15–19, 1960, sponsored by National Academy of Sciences—National Research Council. Edited by Milton Burton, Chemistry Department and Radiation Laboratory, University of Notre Dame; J. S. Kirby-Smith, Biology Division, Oak Ridge National Laboratory; and John L. Magee, Chemistry Department and Radiation Laboratory, University of Notre Dame. Cloth. Price, $8.50. Pp. 426. John Wiley & Sons, Inc., 440 Fourth Ave., New York 16, N. Y., 1960.

A CLINICAL PROSPECT OF THE CANCER PROBLEM. Introductory Volume, Monographs on Neoplastic Disease. General Editor, D. W. Smithers, M.D., F.R.C.P., F.F.R., Professor of Radiotherapy in the University of London; Director, Radiotherapy Department, Royal Marsden Hospital, and Institute of Cancer Research, Royal Cancer Hospital; Radiotherapist, Brompton Hospital. Cloth. Pp. 232, with 46 illustrations. E. & S. Livingstone, Ltd., 16–17 Teviot Place, Edinburgh 1, Scotland, 1960.

LUMBAR DISCOGRAPHY AND LOW BACK PAIN. By Donald deForest Bauer, M.D., C.M., M.Sc., Consulting Radiologist, Klamath Valley Hospital and Hillside Hospital; Associate Supervisor and Radiologist, Department of Medical X-Ray Technology, Oregon Technical Institute, Klamath Falls, Oregon. Cloth. Price, $5.00. Pp. 89, with 32 illustrations. Charles C Thomas, Publisher, 301–327 E. Lawrence Ave., Springfield, Ill., 1960.

THE BASIC PHYSICS OF RADIATION THERAPY. By Joseph Selman M.D., Clinical Assistant Professor of Radiology, The Southwestern Medical School, University of Texas; Director, School of X-Ray Technicians, Tyler Junior College; Chief of Radiology Service, Medical Center Hospital; Attending Radiologist, Mother Frances Hospital; Consultant in Radiology, East Texas Tuberculosis Hospital, Tyler, Texas. Cloth. Price, $14.50. Pp. 671. Charles C Thomas, Publisher, 301–327 E. Lawrence Ave., Springfield, Ill., 1960.

OCCUPATIONAL DISEASES AND INDUSTRIAL MEDICINE. By Rutherford T. Johnstone, M.D., Consultant in Industrial Medicine; Clinical Professor of Preventive Medicine and Public Health; Clinical Professor of Medicine, University of California at Los Angeles; and Seward E. Miller, M.D., Director, Institute of Industrial Health; Professor of Medicine, Medical School, University of Michigan; Professor of Industrial Health, School of Public Health, University of Michigan. Cloth. Pp. 482. W. B. Saunders Co., 218 W. Washington Square, Philadelphia 5, Pa., 1960.

SELECTED PAPERS FROM THE INSTITUTE OF CANCER RESEARCH: ROYAL CANCER HOSPITAL AND FROM THE ROYAL MARSDEN HOSPITAL—1958. Volume 13. Cloth. Pp. 1016. The Chester Beatty Research Institute, Fulham Road, London, S. W. 3, England, 1960.

THE NORMAL SKULL; A ROENTGEN STUDY. By Robert Shapiro, M.D., Chairman, Department of Radiology, Hospital of Saint Raphael, New Haven; Associate Clinical Professor of Radiology, Yale University School of Medicine; and Arnold H. Janzen, M.D., Assistant Radiologist, Hartford Hospital, Hartford; Former Chairman, Department of Radiology, Grace-New Haven Community Hospital and Yale University School of Medicine, New Haven. Cloth. Price, $18.00. Pp. 257, with 645 illustrations. Paul B. Hoeber, Inc., 49 E. 33rd St., New York 16, N. Y., 1960.

DIE CHIRURGIE DES MAGENSARKOMS. By Prof. Dr. A Gütgemann, Direktor der Chirurgische, Universitätsklinik und Poliklinik, Bonn; and Dr. H. W. Schreiber, Wissenschaftl. Assistent an der Chirurgische, Universitätsklinik und Poliklinik, Bonn. Paper. Price, $6.80. Pp. 95, with 31 illustrations. Georg Thieme Verlag, Herdweg 63, Stuttgart N, Germany, 1960. In the United States and Canada, Intercontinental Medical Book Corporation, New York 16, N. Y.

DIE OCCIPITALE DYSPLASIE. By Doz. Dr. H. Schmidt and Dr. E. Fischer, Medizinisches Strahleninstitut der Universität Tübingen. Paper. Price, $8.35. Pp. 69, with 69 illustrations. Georg Thieme Verlag, Herdweg 63, Stuttgart N, Germany, 1960. In the United States and Canada, Intercontinental Medical Book Corporation, New York 16, N. Y.

LA RADICULOGRAPHIE LOMBAIRE DANS LA SCIATIQUE. By J. Ecoiffier, Radiologiste des Hôpitaux de Paris. Paper. Pp. 140, with 51 illustrations. Masson et C^{ie}, Éditeurs, 120 Boulevard Saint-Germain, Paris 6^{e}, France, 1960.

LA STRATIGRAFIA NELLA PATOLOGIA DEL MEDIASTINO. By G. L. Besio; P. de Albertis; P. Pierotti; and M. Scursatone. Cloth. Price, L. 5,500. Pp. 254, with 171 illustrations. Società Editrice "Universo," Via G. B. Morgagni 1, Rome, Italy, 1960.

MODERN TRENDS IN DIAGNOSTIC RADIOLOGY (Third Series). Edited by J. W. McLaren M.A., M.R.C.P., F.F.R., D.M.R.E., Radiologist, X-Ray Department, St. Thomas' Hospital, London; Examiner in Radiology to the Examining Board of England and to Edinburgh University; sometime Examiner in Radiology, University of London and Faculty of Radiologists. Cloth. Price, $16.00. Pp. 285, with 209 illustrations. Paul B. Hoeber, Inc., 49 E. 33rd St., New York 16, N. Y., 1960.

RADIATION THERAPY OF EARLY PROSTATIC CANCER. A Monograph in American Lectures in Urology. Publication number 399 in the American Lecture Series. By R. H. Flocks, M.D. and D. A. Culp, M.D., both of the State University of Iowa Department of Urology, Iowa City, Iowa. Charles C Thomas, Publisher, 301–327 E. Lawrence Ave., Springfield, Ill., 1960.

VOL. 85, NO. 1

ABSTRACTS OF RADIOLOGICAL LITERATURE

Department Editor: T. LEUCUTIA, M.D., Harper Hospital, Detroit 1, Michigan

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ROENTGEN DIAGNOSIS

NECK AND CHEST

BASU, S. P. Radiological appearance in the lung fields of tropical eosinophilia. *Calcutta M. J.*, May, 1960, *57*, 152–156. (From: School of Tropical Medicine, Calcutta, India.)

Tropical eosinophilia appears to be a clinical entity but the etiology is unknown. Roentgenologically it is identical with Loeffler's syndrome. The author studied the chest roentgenograms of more than 400 cases of tropical eosinophilia. The most common abnormality was an increase in the vascular markings. This occurred in 67 per cent of the patients and was usually associated with prominent hilar shadows. The next most common abnormality was a mottling of the lung fields, occurring in 31 per cent of the patients. The densities varied in size from 2 to 5 mm., were usually poorly circumscribed, and were irregular in outline. The author feels that a variation in the size of the densities is typical of tropical eosinophilia and helps differentiate it from other diseases such as sarcoidosis, pneumoconiosis, and miliary tuberculosis. Fine densities and large patchy shadows were uncommon. The lungs had a normal appearance in only 2 per cent of the patients with tropical eosinophilia.

The course of the disease was variable. Roentgen improvement tended to be slow and did not necessarily keep pace with the clinical improvement of the patient. In many instances follow-up roentgenograms showed a further increase in the abnormal densities, even though the patient had become symptom free and the eosinophil count was dropping. Improvement tended to occur first in the peripheral lung fields, while the prominent hilar shadows returned to normal more slowly or remained permanently enlarged. Only 25 per cent of the cases showed normal chest roentgenograms within six weeks. Recurrences of symptoms and roentgen abnormalities were common, even after a remission of months or years.—*F. L. Williams, M.D.*

FLAHERTY, ROBERT A., KEEGAN, JAMES M., and STURTEVANT, HARWOOD N. Post-pneumonic pulmonary pneumatoceles. *Radiology*, Jan., 1960, *74*, 50–53. (Address: R. A. Flaherty, Lutheran Hospital, Fort Wayne, Ind.)

The authors report 20 cases in which pulmonary pneumatoceles developed as a complication of pneumonia and they discuss the mechanism of development, the roentgen appearance and the ultimate prognosis. Eight of the reported cases were children and 12 were adults. The etiologic factor in most cases in both age groups was staphylococcal pneumonia.

The pneumatoceles are thin-walled, air-containing, cyst-like structures. They are believed to be the result of localized obstructive emphysema secondary to inflammatory narrowing of a bronchus. The most significant feature in patients with pulmonary pneumatoceles is the absence of symptoms after the pneumonia subsides and the pneumatocele remains. Eighteen of the 20 patients in the authors' series were completely asymptomatic at the time the pneumatocele was fully developed. When first identified, a pneumatocele appears as a small air space within the area of pneumonitis. As it enlarges, the wall may appear thick but the degree of thickness cannot be determined accurately because of the surrounding pneumonia. As the pneumonia resolves, the typical thin-walled cyst appears. The pneumatoceles may be single or multiple. They may contain fluid but usually are completely air-filled. Usually they disappear in a period of weeks or months following their onset, leaving a thin fibrotic strand in the area.

Pneumatoceles occurring in infants must be differentiated from congenital cysts of the lung and lobar emphysema. When a pneumatocele occurs in an adult, it may be confused with the thin-walled cavities which can occur in the mycotic infections. The clinical course and the recovery of *Staphylococcus aureus* in the early stage of the inflammatory process are the best means of differentiating pneumatoceles from cavities of a more serious nature —*Arno W. Sommer, M.D.*

SCATLIFF, JAMES H., KUMMER, ALFRED J., and JANZEN, ARNOLD H. The diagnosis of pericardial effusion with intracardiac carbon dioxide. *Radiology*, Dec., 1959, *73*, 871–883. (Address: J. H. Scatliff, Yale-New Haven Medical Center, Hew Haven 4, Conn.)

The limitations of plain roentgenography, kymography, and fluoroscopy, and the added hazard when opaque angiography and pericardiocentesis are used to establish the diagnosis of pericardial effusion, are recognized. Intracardiac insufflation of carbon dioxide into the right atrium as a means of differentiating pericardial effusion from cardiac enlargement and pericarditis as reported by others has been evaluated in a group of 22 patients, correlating the findings with the clinical course or subsequent autopsy findings.

With the patient in the left lateral decubitus position, an injection of 50 to 100 cc. of gas is made over a two to three second interval into the antecubital vein. The carbon dioxide, once in the right atrium, rises and outlines its uppermost surface. The opaque shadow or band outlined between the carbon dioxide bubble and the overlying lung consists of pleura, pericardium, and atrial wall. The thickness of this band can then be recorded and measured by appropriate roentgenographic procedures. Normally the shadow should be no more than 5 mm. thick. In the presence of pericardial effusion, the heart assumes a dependent position and the fluid, if freely mobile and in sufficient quantity, widens the space

between the pericardium and atrium producing a widened opaque band. In the large dilated heart the right atrial wall remains of normal size or its thickness is only slightly increased. Therefore, it is possible in most instances to differentiate between cardiac enlargement and significant pericardial effusion; however, there is a zone, roughly between 5 and 20 mm., which may represent pericardial effusion, pericarditis, or both. Asymmetry of the opaque band suggests effusion, whereas constant uniform thickness of the opaque band and flattening of the dome of the gas bubble by the relatively inelastic pericardium indicate pericarditis. These findings are in general agreement with opaque angiographic studies reported by others.

Confusing shadows, unless recognized as such, may be produced by the presence of gas in the vena cava and hepatic veins, the opaque density of the blood-filled left atrium overlying the right atrial gas shadow, the appearance of a compartmentalized gas shadow due to some of the gas collecting in a smaller volume of atrium above the crista terminalis, the appearance of a heavily trabeculated atrial appendage, the presence of a gas bubble under a tricuspid valve in the right ventricle, and the presence of the shadow of a superimposed intermediate bronchus or ramifying pulmonary vessels. Pericardial disease such as benign or malignant tumors, metastases, multiple myeloma, sarcoidosis, or amyloid infiltration, if present in the region of the right atrial wall, may displace the gas bubble, giving a false positive finding of fluid. Lesions within the right atrium such as tumor or thrombus will also produce an abnormal outline in the opaque band. In such cases opaque contrast studies may be indicated, where opacification of all the cardiac chambers will give more information regarding the extent of the lesion than the localized carbon dioxide study. Pulmonary infiltration in the vicinity of the right atrium or mobile right pleural fluid will obviate accurate assessment of the opaque band.

Initially the patients were turned into the supine position at the conclusion of the examination, usually twenty to thirty seconds after the injection. One of the 15 patients manipulated in this fashion developed an episode of paroxysmal coughing lasting for thirty minutes. This was the only one in the entire series in whom any complication was manifested The results of experimental studies on two dogs in which the nitrogen content of the bubble and femoral artery pressures were measured seem to indicate the possibility of embolism or hypotensive effects developing when the patient is turned on his back. Consequently the patients are now maintained in the left decubitus position after injection until complete resorption of the gas bubble has been checked after five minutes.

Possibly the only contraindication to carbon dioxide examination is the presence of a known large intracardiac shunt; however, even this is doubtful. A further limitation of the technique is the necessity of placing the patient in the left decubitus position and maintaining that posture for at least ten minutes. If chronic lung disease or congestive failure is present, a preliminary trial in the left decubitus position may be made to check for development of unusual pulmonary symptoms.

Several case reports are presented to illustrate the value of this procedure.—*Walter H. Jarvis, Jr., M.D.*

Abdomen

Hiemsch, W. Zur Methodik der röntgenologischen Funktionsprüfung operierter Mägen. (A method for roentgen study of gastric function in the postoperative stomach.) *Fortschr. a. d. Geb. d. Röntgenstrahlen u. d. Nuklearmedizin*, April, 1960, *92*, 395–401. (Address: Ev. Diakonissenanstalt, Hemmstr. 124/126, Bremen, Germany.)

Roentgen observation of 55 patients with gastroenterostomies showed that ordinary barium passed rapidly through the gastric stump and resulted in an inadequate study of the function of the gastroenterostomy. When the following mixture was used—1 slice of white bread (about 50 gm.) in 100 cc. of milk and barium sulfate suspension ad 200 gm.—the appearance of the gastric stump was markedly changed. It became dilated like an atonic balloon and then emptied slowly in gradual spurts, so that the outline and mucosal pattern of the gastric stump as well as the proximal small bowel could be satisfactorily studied. Thus the mixture more closely approximates the conditions that obtain when food is taken. Fewer cases of "dumping" were found with this method.—*J. Zausner, M.D.*

Pyle, Roger, and Samuel, Eric. An evaluation of the hazards of barium enema examinations. *Clinical Radiology*, July, 1960, *11*, 192–196. (From: Department of Diagnostic Radiology, Royal Infirmary, Edinburgh, Scotland.)

The widespread use of barium enema examinations has resulted in such familiarity with the procedure that a false sense of security has developed; a careful appraisal of the potential dangers of the investigation is made all too infrequently. As the examination is extensively used for exclusion of malignant disease, it naturally follows that many of the patients are elderly and frail and this in itself constitutes a special hazard.

Injury to the bowel wall from an incorrectly inserted enema tube is the most common complication. The only tube which should be inserted blindly into the rectum is a soft rubber one, and even this has been reported to perforate apparently healthy bowel. Where there is a colostomy, it may be necessary to administer the enema through it, and this is

another potential source of danger, as damage to the colon and perforation are more frequent in these cases than in a normal rectum. Safeguards against perforation are: the use of a rubber catheter, the use of a teat from a feeding bottle, to which the catheter is threaded and which is kept centrally in the stoma, the avoidance of force with the removal and reinsertion of the tube should any difficulty be encountered, and insertion of the catheter to the minimum distance compatible with adequate filling. Under normal circumstances, using the gravity tank method of administration with the can at three feet, perforation from hydrostatic pressure may only occur in a diseased bowel. The high mortality associated with perforation should be an adequate warning against the temptation to raise the fluid reservoir higher to obtain a more rapid flow.

Another serious complication of the enema is "water intoxication." Water retained or absorbed without electrolyte can lower the osmolarity of the body fluid and cause severe symptoms which are mainly cerebral. Water intoxication has been not infrequently reported in cases of megacolon, and there have been several fatalities reported. Prevention of water intoxication by raising the osmotic pressure of the administered fluid by the addition of salt has been recommended and is simple to do; also, a saline solution is considered to be simple and safe in the absence of renal and cardiac insufficiency. Barium enema in megacolon should be allowed to proceed only until the dilated segment is reached, at which stage the enema should be stopped.

In a large series of barium enema examinations investigated by Zhentlior, Lassar and Rigler, perforation of the bowel was found to occur relatively more frequently under three circumstances: (1) when the enema was performed by way of a colostomy stoma; (2) when an inflatable balloon was used; and (3) when the examination followed shortly after endoscopy. Intestinal obstruction due to the impaction of barium sulfate and feces into hard masses occasionally occurs. Ulcerative colitis carries a greater risk of perforation of the bowel, and barium enema in this condition should be most carefully and slowly administered. The use of a self-retaining inflatable Foley catheter counteracts leakage of the fluid from the rectum during the filling, but the air pressure should not exceed 25 mm. Hg within the bag. With the addition of tannic acid to the enema fluid to promote good evacuation for a mucosal relief study, concentrations of 0.5 per cent have given rise to abdominal pain and colic, and a concentration of 1.0 per cent has been followed by vasomotor collapse and shock.

Brown and Fine in 1941 reported an unusual complication when, during air insufflation for double contrast, air was seen to enter the retroperitoneal space. Retrosternal mediastinal emphysema and surgical emphysema in the neck developed, but the symptoms and signs cleared completely several days later. The authors report a similar case in which little or no air remained in the bowel lumen, most of it accumulating in the retroperitoneum. Twelve hours later surgical emphysema was noted in the neck and roentgenograms revealed a retroperitoneal pneumogram. Air was present under the diaphragm and in the mediastinum and neck. On sigmoidoscopy, at 10 cm. there was a small area of proctitis, which, in the opinion of the endoscopist, was compatible with a perforation of the posterior rectal wall at this point. However, the collapsed mucosal pattern of the rectum on the insufflation roentgenogram suggested that perforation had occurred within 5 cm. of the anus. Uneventful recovery occurred.—*Samuel G. Henderson, M.D.*

BRUNTON, F. J. Retroperitoneal emphysema as a complication of barium enema. *Clinical Radiology*, July, 1960, *11*, 197–199. (From: The Diagnostic Radiological Department, St. Mary's Hospital, London, W.2, England.)

The better known complications of barium enema examination include intraperitoneal perforation of the bowel, fatal intravasation, water intoxication and barium granulomata of the rectum. Retroperitoneal emphysema, although less well known, is a recognized complication of sigmoidoscopy and of rectosigmoid surgical operations. The author describes a case of widespread interstitial emphysema following air insufflation in an elderly woman with diverticulitis.

The air leakage occurred during the insufflation, but the exact site was not ascertained. The possibility of rectal injury by the nozzle of the syringe or by a balloon obturator (used to retain the barium enema) is considered. Another possibility is that a diverticulum or mural abscess was perforated low in the sigmoid. Retroperitoneal emphysema developed and air was present in the perirectal area. Later, subcutaneous emphysema was noted in the upper chest and neck, and air was seen also in the mediastinum. The patient was treated with intramuscular penicillin and streptomycin initially, and later with oral terramycin. She remained afebrile and the air was gradually absorbed within a period of a week. She suffered no other ill effects.—*Samuel G. Henderson, M.D.*

ELSON, MATTHEW W. Antemortem radiographic demonstration of gas gangrene of the liver. *Radiology*, Jan., 1960, *74*, 57–60. (Address: University Hospital, 11th and Neil Aves., Columbus 10, Ohio.)

The author presents what appears to be the first reported case of gas gangrene of the liver with positive roentgenographic findings observed before death. The patient's clinical history and the physical and autopsy findings are described in detail. Posteroanterior roentgenograms of the chest and a supine roentgen examination of the abdomen showed numerous isolated and confluent clusters of gas bubbles,

corresponding in location to the entire right lobe of the liver, along with a small amount of free air beneath the right leaf of the diaphragm. Death ensued shortly after the roentgenologic examination. The roentgenographic findings were subsequently confirmed at autopsy.

Many investigators have demonstrated that gram-positive anaerobic spores are extensively distributed in nature and that they are relatively avirulent. They require an ideal environment to become pathogenic. The author presents this report of clostridial infection in the liver of a diabetic patient to demonstrate that gas gangrene may develop in the liver prior to death.—*W. M. McBride, M.D.*

POZNANSKI, ANDREW K. Cyst of the left triangular ligament of the liver. *Radiology*, Dec., 1959, *73*, 896–897. (Address: Henry Ford Hospital, Detroit 2, Mich.)

A study of the literature by the author revealed only 7 cases in which a cyst was located in one of the hepatic ligaments. In 4 of these 7 cases the cyst was located in the hepatic ligament, and in the other 3 cases in the ligamentum teres. These cysts may be classified as primary or secondary. Primary cysts may be of lymphangitic origin, or due to a developmental defect, or the result of peritoneal inclusion. The symptoms are variable, but a number of the patients have pain in the epigastric region, indigestion, or a full feeling more marked after meals. While the size of the cysts is variable, they are usually large and palpable. In a few of these cases roentgen examination of the gastrointestinal and renal systems was done, and in several instances an extrinsic pressure defect of the gastrointestinal tract was noted. Pathologically, the cyst in most cases was unilocular with a smooth endothelial lining and was filled with a clear or slightly cloudy serous fluid.

The author presents a brief review of the literature and reports 1 additional case in which the location of the cyst was in the triangular ligament of the liver. The cyst produced an indentation upon the stomach filled with barium and air. The indentation was shown by pneumoperitoneum to be a mass that was separate from the stomach and the diaphragm except for a fibrous attachment to the latter.

This cyst differed from the others which have been reported in its location and the fact that it contained hepatic tissue. None of the cysts were diagnosed prior to surgery.—*W. M. McBride, M.D.*

CAROLI, J., PORCHER, P., PEQUIGNOT, G., and DELATTRE, M. Contribution of cineradiography to study of the function of the human biliary tract. *Am. J. Digest. Dis.*, Aug., 1960, *5*, 677–696. (From: University of Paris and Saint Antoine Hospital, Paris, France.)

The authors studied by cineroentgenography the function of the common bile duct and the conditions of reflux into the duct of Wirsung. The cineroentgenograms were correlated with manometric studies carried out through an indwelling T-tube. Thirty-five per cent diodone was the contrast agent. The pressures were controlled and a synchronizer permitted determination of the pressure employed at the time of each roentgenogram.

The kinetics of contraction of the sphincter of Oddi were studied. The most frequent type of contraction was "antiperistaltic" in which the contraction wave moved from the ostium to the common duct. The opening of the sphincter was the reverse of this process, the widening starting at its superior point and progressing downward. In 1 of their patients the cineroentgenograms showed the mechanism of pseudocalculus formation in the lower common duct. Strong contraction of the sphincter caused the opaque medium to disappear completely. However, the pressure of the injection caused a dilatation of the distal common duct just above the sphincter. The lower border of the opaque medium was concave downward and simulated an ovoid filling defect.

The cineroentgenographic studies demonstrated that relaxing agents such as atropine sulfate changed the rhythm of contraction and relaxation, the sphincter remaining open for a longer period of time and closed for a shorter period. Morphine had an opposite effect.

The sphincter of Oddi was shown to be capable of autonomous muscular action, but its contraction could also be initiated when a duodenal wave reached the region of the ostium.

The cineroentgenographic studies demonstrated reflux into the duct of Wirsung in 30 per cent of the patients. When the anatomic features of the duct of Wirsung were normal, there was a higher incidence of reflux when the common duct pressure was increased or when the region of Oddi was relaxed by drugs or by a fatty meal. This was not true when the anatomic conditions were abnormal.—*J. L. Williams, M.D.*

GYNECOLOGY AND OBSTETRICS

BENNETT, ROBERT. Unequivocal radiological evidence of intra-uterine foetal death, including demonstration of gas formation within the foetal circulation: report of a case, and review of thirty-seven cases of foetal death. *Clinical Radiology*, July, 1960, *11*, 200–204. (From: King Edward Memorial Hospital for Women, Perth, Australia.)

Various signs of intrauterine fetal death which have been described include the following: (1) overriding of the skull bones with cephalic asymmetry (Horner, 1921; Spalding, 1922); (2) disproportion between fetal maturation and the estimated period of gestation; (3) absence of continued fetal growth with serial roentgenographic examinations; (4) absence of change in position of the fetus and particularly of its

extremities on serial roentgen examination; (5) formation of an angular kyphos in lumbar or dorsal spine; (6) collapse of thoracic cage; (7) roentgen evidence of gas in fetal circulation (Roberts, 1944); (8) the "halo sign," described by Deuel in 1947, due to increase in the width of the soft tissues between the radiolucent subcutaneous fat of the scalp and the bones of the fetal cranial vault; (9) disalignment of fetal skull bones at the coronal and lambdoid sutures prior to the tenth lunar month of pregnancy and in the absence of labor pains (Borell and Fernstrom, 1958). Such disalignment must occur before overlapping of the cranial bones is possible.

Gas in the fetal circulation appears early in comparison with other roentgen signs and may be seen within three days of the estimated time of death. Definite demonstration of such gas is an irrefutable sign of fetal death. If gas is present in sufficient quantity and in branching vessels and is unobscured by confusing shadows (such as maternal bowel gas, radiolucent fat layer of maternal psoas muscle, well-developed fetal subcutaneous fat layer around the extremities), it may at once be recognized by its bizarre appearance like gas in the biliary tree. This appearance is produced by gas in the portal vessels. Gas in umbilical vessels also will produce a characteristic shadow, sometimes with a round "end-on" appearance of the coiled vessels. Gas in the fetal heart can readily be identified by its position in the fetal thorax and its roughly triangular shape with the base caudad. The main dorsal vascular trunks produce characteristic parallel-walled and fairly wide gas streaks following the curve of the fetal spine.

A case is reported in which evidence of fetal intravascular gas and Deuel's halo sign were present, permitting unequivocal roentgenologic confirmation of fetal death. A review of roentgenograms of 36 patients who underwent prepartum roentgenographic examination showed evidence of fetal intravascular gas formation in 5. This review showed that Spalding's sign (overlapping of cranial bones) and evidence of lack of fetal tone were the most consistently helpful roentgen signs in arriving at a diagnosis of fetal death.—*Samuel G. Henderson, M.D.*

Genitourinary System

BÉRAUD, CL., DEFFRENNE, P., and BRESSIEUX, R. Intérêt de la tomographie dans l'urographie du nourrisson et de l'enfant. (The value of laminagraphy in urographic studies of infants and children.) *J. de radiol., d'électrol. et de méd. nucléaire*, May, 1960, *41*, 230–235. (From: Clinique médicale infantile et Service de Radiologie, Hôpital Debrousse, 35 Chemin Saint-Irénée, Lyon-5e, France.)

Laminagraphy performed during urographic procedures may give important information which could not be obtained by other methods.

Many difficulties are encountered during urography in infants. For introduction of the iodine medium, venous injection by epicranial or jugular puncture is recommended and has been used in all the cases of the authors. A dose of 4 to 10 cc. of a 25 per cent tri-iodinated solution was found to be practical. Subcutaneous or intramuscular injection with hyalorunidase is painful, favors air-swallowing and is to be avoided. The presence of gas in infants, particularly in those with infection, is an objection to the use of abdominal compression. The administration of an antihistaminic drug is valuable for its quieting effect. Compression is not used to minimize agitation and this is compensated for by employing a cephalad Trendelenburg position which helps to keep the opaque medium more dense in the pyelocalyceal cavities.

As regards the laminagraphic technique, the indication for it depends on what is being looked for and what has been revealed in the earlier urographic roentgenograms. Its use is preferred in cases of abdominal distention in infants. The method consists of obtaining an early excretory roentgenogram taken after three minutes with fixed grid and high kilovoltage at 2/100 second. Then laminagrams are taken, more to evaluate the anatomic status than to study the renal function. Late laminagrams made in cases of renal anomalies are valuable for study of the ureters and bladder. The depth for useful laminagrams is from 3 to 5 cm. from the dorsal plane. The constant factors for a manual laminagram of an eight month old infant are 0.3 sec., 64 kv. and 100 ma. Automatic laminagraphy has been done at 1.0 second and with a 38° angle. In older and more cooperative children, an angle of 45° is preferred. To reduce radiation hazards, when standard urography is sufficient, routine laminagraphy should be omitted; however, in infants the expected results justify the systematic use of laminagraphy.

Among the great advantages of urolaminagraphy are the effacement of abdominal gases and the sharp delineation of renal contours. The spine may be studied for malformations and often the ureters can be seen in their full length, being located less than 1 or 2 cm. anterior to the renal plane. However, concretions of nephrocalcinosis are too fine to be visualized.

In conjunction with 281 urographic examinations performed in two years in their pediatric service, the authors made 52 excretory laminagrams, of which 31 were of children two years of age and 21 of children ranging in age from two to ten years. Laminagraphy was of decisive help in 3 children over two years of age, and in 12 children less than two years old.

If laminagraphy is to be systematically used in infants, the authors recommend it in children affected with myxedema, renal infection or insufficiency or in those with a dilated colon. In cases of tumor of the left hypochondrium, urolaminagraphy will differentiate an enlarged spleen from a big kidney, thus

avoiding the need of a retropneumoperitoneum.—*H. P. Lévesque, M.D.*

Squire, Lucy Frank, and Schlegel, Jorgen U. Pyelography in renal disease with hypertension; correlation between pyelographic findings and differential renal function studies. *Radiology*, Dec., 1959, *73*, 849–864. (Address: L. F. Squire, Strong Memorial Hospital, Rochester 20, N. Y.)

Experience over the past thirty years has shown that certain cases of hypertension are related to renal disease and that this hypertension may be curable if recognized before the heightened pressure becomes fixed. Studies have shown that a relative renal ischemia of still viable parenchyma may be the cause of this type of hypertension and that, in some cases, removal or repair of the guilty kidney tissue may result in a cure.

The purpose of this paper is to alert the radiologist to the limitations of the role he can play in helping the clinician select the salvageable patient. Seventeen hypertensive patients in whom complete studies were done are reported, with special emphasis on the correlation of intravenous pyelograms with differential kidney function studies. In all but 1 of these patients, excretion of the opaque medium was of good density on both sides, in spite of striking unilateral or bilateral depression of function, showing that the intravenous pyelogram is not helpful in indicating a malfunctioning kidney in the absence of morphologic changes. Furthermore, additional pyelographic findings, blood chemistry, urine and conventional function studies were often found to be normal in patients with renal ischemia due to some type of arterial obstruction. Causes of this obstructive arterial disease include: aberrant arteries, renal artery aneurysm, obstruction due to embolus, thrombosis, plaques and intimal proliferation, renal infarct, constriction of arteries in scar tissue secondary to trauma, and pyelonephritis.

The authors feel that, where no known contraindication exists, aortography should be performed in hypertensive cases in addition to differential kidney function tests with catheters in both ureters and simultaneous measurement of inulin clearance (glomerular filtration rate), volume in cubic centimeters per minute, and P.A.H. (para-aminohippuric acid) clearance (renal flow). Such studies often indicate depression of function on one side in the salvageable patient when all other means of discovering unilateral renal disease have failed, or they may prove the presence of bilateral disease, which would preclude operative intervention on the kidneys. The functional state of the good kidney may also be established by these studies.—*Donald N. Dysart, M.D.*

Brown, J. J., Owen, K., Peart, W. S., Robertson, J. I. S., and Sutton, D. The diagnosis and treatment of renal-artery stenosis. *Brit. M. J.*, July 30, 1960, *2*, 327–338. (From: St. Mary's Hospital, London, England.)

This paper constitutes a complete and thorough discussion of the problem of renal artery stenosis and is based upon the study of 22 patients. The disease is discussed with reference to clinical features, etiology, incidence, family history, pathology, diagnostic techniques, treatment and results. The roentgenologic aspect is covered in a discussion of the plain roentgenographic, intravenous pyelographic and retrograde aortographic findings.

The most common cause of renal artery stenosis is the atheromatous plaque. The ages in the present series ranged from seventeen to sixty-five years, the largest number being in the older group. A large percentage of the patients was found to have concurrent evidence of disease elsewhere, *i.e.*, intermittent claudication, ischemic heart disease, stroke, etc. A positive family history was only occasional. Physical examination and laboratory work may reveal hypertension, abdominal bruit, hypertensive retinal changes, polyuria, hypokalemia, proteinuria, and increased leukocyte excretion rate.

Special investigations in this disease include independent ureteric catheterizations and urinalysis for volume, sodium concentration, chloride concentration, inulin, creatinine and P.A.H. clearances and concentrations. In renal artery stenosis, output is decreased, concentration of sodium and chloride is decreased, clearance of inulin, creatinine and P.A.H. is inhibited and urinary concentrations of these substances are increased.

In many cases of renal artery stenosis, the kidney is noted on the plain roentgenogram to be smaller than the opposite. Intravenous pyelography is helpful in that the affected kidney, because of its increased concentration of inulin, concentrates the contrast medium better than the normal kidney. As a result, the affected kidney shows better contrast on an intravenous pyelogram than does the normal kidney. In cases of severe damage, however, this no longer holds true and poor function will be evident.

Selective retrograde aortography, using a variation of Ödman's technique, was used to investigate the size of the renal arteries. Using this method, 5 cc. of hypaque or urografin was injected directly into the renal artery. On occasion, injection of the contrast medium into the aorta was also done, on withdrawal. It was noted that the tip of the catheter caused stress phenomena which often had the appearance of stenosis.

Surgical correction should be undertaken only after intra-arterial pressures are taken to determine a pressure-drop across the stenosis.

Corrections should be limited to reconstruction if possible, and nephrectomy should be performed only if necessary. No operative deaths were encountered and 5 out of 6 operated patients experienced marked

resolution of their hypertensive disease. Pathologic studies of the affected kidneys showed tubular damage to be the most constant finding.

The details of all cases are tabularized.—*W. C. MacCarty, Jr., M.D.*

ZHEUTLIN, NORMAN, HUGHES, DIXON, and O'LOUGHLIN, BERNARD J. Radiographic findings in renal vein thrombosis. *Radiology*, Dec., 1959, *73*, 884–890. (Address: N. Zheutlin, University of California Medical Center, Los Angeles 24, Calif.)

The clinical syndrome of renal vein thrombosis occurs most frequently in children, over 50 per cent of the patients being less than five years of age. Ileocolitis is considered to be the chief predisposing cause in the young. In adults the condition may be secondary to thrombosis of the inferior vena cava with extension into the renal veins. Malignant growths of the kidney produce occlusion by direct invasion or by extrinsic pressure. In some reported cases, primary renal disease such as amyloidosis, glomerulonephritis, and malignant hypertension has produced thrombosis of the renal vein. There are few clinical cases in which a definite diagnosis is made. Although the roentgenographic findings reported to be associated with the syndrome are bizarre, they are not incompatible with the disease. It is possible to postulate different degrees of progression in vein thrombosis, producing gross changes in the kidney parenchyma and resulting in variable roentgenographic patterns. Thus, in acute thrombosis with massive infarction and perirenal hemorrhage, the intravenous pyelogram will show an enlarged nonfunctioning kidney. The retrograde pyelogram then shows the diffusion of the contrast agent into the kidney mass with an amorphous distribution of density. When one encounters a chronic, slowly progressive renal vein thrombosis, it is highly likely that adequate collateral circulation will take over the venous function, resulting in a relatively normal kidney. Between these two extremes lie the changes produced by renal edema. Here one may see the "polycystic" deformity and the incomplete and irregular pelvis.

Experimental surgical occlusion of the renal vein in dogs was performed in an attempt to reproduce renal changes. In acute occlusion, retrograde pyelograms made at hourly intervals showed increasing diffusion of the medium into the kidney. Attempts to produce renal changes on urograms in experiments simulating chronic venous occlusion were unsuccessful.

Three cases of renal vein thrombosis in man are briefly summarized. A urogram in one was interpreted as showing a polycystic kidney. In another, roentgenography was reported to show bilateral renal edema.—*Walter H. Jarvis, Jr., M.D.*

GONDOS, BELA. Rotation of the kidney around its transverse axis. *Radiology*, Jan., 1960, *74*, 19–25. (Address: 1720 Connecticut Ave., N. W., Washington, D. C.)

Rotation of the kidney about its transverse axis may be recognized on anteroposterior abdominal roentgenograms or urograms. The kidney is normally held in position by the fatty capsule, the renal fascia, the support of adjacent organs, intra-abdominal pressure, and the vascular pedicle. An increase in size of one or more of the adjacent organs, or a change in position, may cause encroachment upon the space available for the kidney, thus forcing the kidney to try to accommodate itself with a shorter diameter in the direction of encroachment. The vascular pedicle acts as a fulcrum and the lower pole is tilted anteriorly. This almost exclusive direction of rotation with the lower pole tilted anteriorly can be explained by the relative rigidity and solidity of the structures of the upper abdomen compared with the softer structures of the lower abdomen. The peritoneum has no significant role in rotation, and attempts to localize a mass as to its intra- or retroperitoneal position have been unsuccessful. In rotation around the transverse axis, the space-occupying agent acts on the vertical axis of the body, and it makes no difference whether the liver, gallbladder, spleen, or adrenal gland is the enlarged organ. There is no essential difference, with regard to the encroachment, whether the mass is adjacent to the upper or lower pole or is a tumor of the kidney itself.

Clinically, rotation around the transverse axis may be a useful sign in localization of abdominal masses as it is common with tumors of the kidney, or may be associated with displacement caused by the enlargement of adjacent organs. Recognition of rotation is important to avoid interpreting a blunted "lower pole" as a cyst or tumor, or to avoid incorrectly diagnosing a hypoplastic or contracted kidney. Rotation is also common with a ptosed kidney.—*J. C. Moore, M.D.*

SKELETAL SYSTEM

BROCHER, J. E. W. Konstitutionell bedingte Veränderungen des Wirbelbogens. (Constitutionally caused changes of the vertebral arches.) *Fortschr. a. d. Geb. d. Röntgenstrahlen u. d. Nuklearmedizin*, April, 1960, *92*, 363–380. (Address: Place Claparède 5, Geneva, Switzerland.)

The various parts of the vertebrae arise from different groups of embryonic cells. Those cells which surround the chorda dorsalis ventrally form the chordal process. A dorsal group of cells grows in layers around the medullary tube and forms the neural processes via a cartilaginous phase. The latter may be recognized in a 12 mm. embryo (measured from head to sacrum). In the 70 mm. embryo, perichondral ossification of the vertebral arches takes place. The vertebral body is the only part of the

spine to develop via endochondral bone formation. The form and shape of the vertebral arches vary with the development of the neural tube. When the latter is experimentally removed, the vertebral arches develop hypoplastically. On examination of the entire spine, it is apparent that there is a proportional relationship between the form and size of the pedicles, the extent of the pars interarticularis, the posterior portion of the arch, and the articular process. These relationships vary with the spinal region as well as with the constitutional type of the individual. Pathologic changes which occur in the vertebral arches differ and sometimes are in sharp contrast to alterations in other osseous segments of the spinal column.

The greatest portion of the osseous-ligamentous border of the spinal canal consists of the vertebral arch. Only at the level of the atlas is the anterior border formed by the transverse ligament, whereas from C2 to L5 it is formed by the posterior wall of the vertebral body or the intervertebral disk, respectively. The lateral borders of the spinal canal are made up as follows: at the atlas, by the lateral masses; at C2 to C6, chiefly by the laminae; at C7 and D1, by the pedicle (one-third) and the laminae (two-thirds); at D2 to D12, mainly by the pedicle; at L1 to L4, one-half by the pedicle and laminae, each; at L5, one-third by the pedicle and two-thirds by the laminae. The posterior borders consist of the medial portion of the laminae.

The shape and size of the spinal canal vary at different levels of the spine. From C1 to C7, it is one-half the size of the corresponding arches; from D1 to D12 it is practically round; from L1 to L4, polygonal; and at L5, triangular. The transverse diameter in the lumbar area is 20–22 mm. and the anteroposterior diameter is 16–18 mm. The normal anteroposterior diameter at the atlas is 22–26 mm. (roentgenogram taken at 150 cm. distance). A decrease of 10 mm. or more suggests spinal cord compression. This measurement is also decreased in atlanto-axial subluxation due to congenital weakness of the transverse or other ligaments. Displacement of the odontoid process may be explained by similar factors. Such congenital abnormalities have not been recorded at any other level from C2 to L5.

The anterior portions of the arch, the pedicles, are particularly important, for example, in the measurement of the interpedicular spaces in spinal cord tumors. Congenitally short pedicles are typically found in chondrodystrophy (achondroplasia). An analogous situation in the rare entity of chondroectodermal dysplasia is described by Caffey. The so-called "extremity dwarf" presents a variety of vertebral malformations: small vertebral body, short pedicles, decrease in interpedicular distance, and a narrow foramen magnum. In the lumbar area, a decrease in the size of the pedicle produces sciatic pain. Butterfly- and hemivertebrae are associated with thick and wide pedicles, examples of the contrasting responses in various parts of the spine. In other words, these anomalies present hyperplasia in one site and hypoplasia in another.

The middle portion, pars interarticularis or isthmus, offers the most frequent examples of congenital defects. The isthmus normally is short, so the axes of the intervertebral joints lie in the same plane. In spondylolisthesis, besides the usual defect, there is lengthening and angulation of the pars interarticularis. It is also lengthened in pseudospondylolysis. These defects are probably due to abnormal resorptive changes on a congenital or constitutional basis. Less common are narrowing, thickening, or sclerosis of the isthmus. Spondylolisthesis may be associated with hypoplasia as well as with abnormality of form and position of the articular process.

The posterior border of the spinal canal consists of the laminae. At birth, the entire vertebral column is open posteriorly. Closure takes place from C3 to C5 at the end of the first year; at C2 at the end of the second year; and at C1 at the end of the fourth year. A physiologic spina bifida is seen in 33 per cent until the seventh year. The most frequent sites for spina bifida are at transitional levels of the spinal column, especially in the lumbosacral region where the incidence is 100 per cent at birth, 81 per cent in the fifth year, 44 per cent in the fifteenth year, and 10 per cent in adults. Spina bifida of the atlas is found in 3 per cent of adults and is best demonstrated by laminagraphic study. Spina bifida may often be associated with a myelocystocele, myelomeningocele, or a meningocele. However, not every patient with a spina bifida and neurologic complaints has one or another of the mentioned anomalies of the spinal canal. A rare defect of the laminae of L5, just posterior to the isthmus, is called a "retroisthmic cleft" and is usually accompanied by a spondylolisthesis of the contralateral side. In cleidocranial dysostosis, spina bifida with wide gaps or delayed closure is common. Hadley described a case of spina bifida of the entire spine in a six month fetus due to failure of the neural process to surround the notochord. This condition is incompatible with life.

Posterior "blocked vertebrae" involve the laminae and spinous process, rarely the intervertebral joint, and never the pedicle. The congenital anomaly differs from the acquired type (postinfectious or posttraumatic), since the latter only involves the body and is usually confined to two adjacent vertebral bodies. Hadley states that a round intervertebral foramen is characteristic of congenitally "blocked vertebrae," whereas it is concha-shaped in the acquired condition.—*J. Zausner, M.D.*

Kolář, J., and Vrabec, R. Röntgenologische Knochenbefunde nach der Hochstromverletzung. (Roentgenologic findings in bones after injury by a high tension electric current.) *Fortschr. a. d. Geb. d. Röntgenstrahlen u. d. Nuklearmedizin*, April, 1960, *92*, 385–394.

(Address: J. Kolář, Radiologische Klinik der Karls-Universität, U nemocnice 2, Praha 2, Tschechoslowakei.)

Routine skeletal surveys and interval examinations will often disclose unsuspected lesions in patients who have been injured by a high tension electric current passing through their bodies. Changes occur at some distance from the actual path of the current as well as at the site of contact. Careful examination is required to detect hairline interruptions of the cortex or minor changes within the osseous architecture. Even these slight changes may not occur until several weeks after the trauma. Jellinek believes that the electric current acts as a mechanical trauma. Jenny advances the theory that an electric splintering in the bone causes an increase in intraosseous pressure due to evaporation of the fluid content of the bone.

The most frequent lesion is a linear or star-shaped fracture with a distinct or indistinct border. Cavitary lesions were found in 3 patients several years after the trauma. Bone necrosis usually has a good prognosis, although occasionally osteomyelitis and sequestration may follow. Periostitis is common and is probably due to infection or inflammation of the soft tissues. Subperiosteal hemorrhage produces changes similar to those in scurvy. Expansion of a phalanx resembling spina ventosa has also been observed. A six year old girl, who sustained an injury by a 220 volt charge, developed spontaneous sloughing of a distal phalanx, the fifth metacarpal and the distal third of the ulna. Neurotrophic changes similar to those in leprosy have been noted in the tips of the extremities.

In younger individuals a variety of developmental changes may occur. These include epiphyseal deformities, alteration of the metaphyses, hypoplasia, and occasionally hyperplasia. The latter may be due to hyperemia in cases of third or fourth degree burns or to the purulent complications. Joint involvement is also fairly common and may result in contractures, complete loss of mobility, subluxation, and, if infection supervenes, destruction of articular surfaces, ankylosis, and spontaneous amputation. Paraarticular calcifications and ossifications have been observed. In 2 cases, after electrical injury osteochondritis dissecans occurred in the head of a metatarsal and metacarpal bone, respectively.

In general, healing progressed satisfactorily within several weeks, even with rather serious atrophy. Occasionally, several years elapsed before complete healing took place, particularly when the necrosis was rather severe. When infection of the soft tissues occurred, the prognosis was less favorable. Several cases required amputation because gangrene had set in.—*J. Zausner, M.D.*

General

Klatte, Eugene C., Campbell, John A., and Lurie, Paul R. Technical factors in selective cinecardioangiography. *Radiology*, Oct., 1959, *73*, 539–547. (Address: E. C. Klatte, 1100 W. Michigan St., Indianapolis, Ind.)

In obtaining over 300 cinecardioangiograms on 16 mm. film in the past two years, various technical details which may critically influence the diagnostic yield of this procedure have been evaluated. The unsharpness factor of the film image can be slightly reduced by using a 0.3 mm. instead of a 1.0 or 2.0 mm. focal spot; however, its use for cine-work is limited by the local heat capacity of the face of the anode. For this reason a 0.5 and 1.0 mm. focal spot combination on a high voltage tube appears most useful at present for cine-work.

Since the field size is a critical limitation in cineroentgenography, the image magnification factor is important. This is primarily a problem of engineering design since the magnification is decreased by increasing the target table-top distance and by decreasing the image tube front input phosphor distance. Also, since some spot roentgenogram devices remove the image tube front away from the patient, there is a distinct advantage in mounting the image tube on the table without interposition of a spot roentgenogram device. Image intensification itself can be used only to decrease radiation dose to a certain level, beyond which film detail suffers significantly. The focal length of the lenses will also alter the size of the film image, and with the limited field size available it is better to frame the entire image so that none of the picture will be cut off. Within these technical limitations one should strive for the fastest lens system possible to assure lower radiation doses.

The greatest and perhaps the only advantage of 35 mm. cineroentgenography is that the larger film frame allows better image detail because the reduction ratio of the original image is critically less than with 16 mm. film; however, cinecardioangiograms of comparable diagnostic yield can be readily produced on 16 mm. films with a significant decrease in radiation dose, cost, and handling problems.

The radiation dose to the patient depends upon many factors. In general, though, the diagnostic yield is much greater and the dose to the patient significantly less than with rapid cassette changers. With proper protection the radiation dose to the operator is less than 1.0 mr per examination. A high quality 16 mm. analyzing projector is necessary to appreciate fully the advantages of the cine-film method in cardioangiography. Also, high quality selective cinecardioangiography depends significantly on the proper catheter, contrast medium, injector, and positioning of the patient. Film with high contrast characteristics and fine grain size is more important in cinecardioroentgenography than high speed characteristics, and Eastman Kodak Linagraphy Shellburst film was found to produce the highest quality cinecardioangiograms. X-ray de-

veloper has been used in processing the film and a 200 foot strip has been successfuly processed in an Eastman Kodak X-Omat by attaching the end of the film to an x-ray film.—*Walter H. Jarvis, Jr., M.D.*

Hodges, Paul C., and Moseley, Robert D., Jr. Cinefluorography employing split-image television type image amplifiers. *Radiology*, Oct., 1959, *73*, 548–556. (Address: P. C. Hodges, 950 E. 59th St., Chicago, Ill.)

The authors describe in detail the roentgen-ray image amplifier recently developed by General Electric Co. This amplifier is a television type amplifier and differs from others in that it is directly sensitive to roentgen rays without the necessity of first converting them into visible light. The construction and operation are discussed and certain important differences between it and the amplifiers of Westinghouse, Philips, Morgan, and Moon are pointed out.

This General Electric image amplifier employs a tube which the manufacturer calls an X-icon. It is simpler than the tubes of Westinghouse and Philips and, unlike them, allows almost any desired amplification of image brilliance plus the advantage of multiple viewing tubes, including one for motion picture monitoring. It is vastly simpler than the Image Orthicon used in Morgan's amplifier and requires only simple and relatively inexpensive electronic circuits for the amplification of its signal.

The authors describe the installation of two of these X-icon image intensifiers in their angiographic laboratory. The installation is such that, with other attached equipment, a biplane split image television type amplifier cineroentgenographic system is produced, which permits the simultaneous display of both frontal and lateral images on each of the kinescope tubes from which the films are made. This equipment has been used for the most part only in experimental animals.—*Donald N. Dysart, M.D.*

Kirkpatrick, John A., and Olmsted, Richard W. Cinefluorographic study of pharyngeal function related to speech. *Radiology*, Oct., 1959, *73*, 557–559. (Address: J. A. Kirkpatrick, St. Christopher's Hospital for Children, Lawrence and Huntingdon Sts., Philadelphia 33, Pa.)

Cinefluorography offers a technique for the visualization of the movements of the palate, tongue, and pharyngeal soft tissues during speech. The apparatus used in this study consists of a conventional fluoroscopic unit, an image intensifier of the electron optical type manufactured by the North American Philips Company, Inc., and a 16 mm. "sound on film" camera (Auricon Cine-Voice II). The camera has a 25 mm. f.95 lens focused at infinity. The fluoroscopic table is placed in the upright position, and the larynx is viewed in the lateral projection. A microphone is held 12 to 18 inches from the patient, and pictures are exposed at the rate of 24 frames per second as the patient speaks. A barium and water mixture is used to demonstrate regurgitation into the nasal cavity. The patient is exposed to a 5 inch circle of radiation for forty-five to sixty seconds, producing 30 to 35 feet of exposed film with 1,000 to 1,500 individual frames available for study.

There is a need for increased knowledge of the motor activities of the lips, tongue, mandible, soft palate, and pharyngeal soft tissues during speech in both the normal and abnormal subject. There are many unanswered questions in relation to muscle activity during speech. Cinefluorography with the synchronous recording of sound is being applied to the investigation of a variety of lesions of the pharynx. It aids in the selection of cases for surgery, and evaluation of different operative procedures. Cinefluorography also aids the prosthodontist by permitting visualization of the prosthesis during speech and evaluation of its functional adequacy. It should lead to more effective speech therapy. It was observed that, when velopharyngeal closure is anatomically impossible, the tongue tends to rise posteriorly (more than in a normal study) to raise the palate. Apparent anatomic apposition of the palate to the posterior pharynx may not connote functional closure, as shown by regurgitation of opaque liquid into the nasopharynx.

Cinefluorography and simultaneous recording of sound promise an elucidation of the relationship of physiology to speech.—*James C. Moore, M.D.*

Miller, Earl R. Cinefluorography in practice. *Radiology*, Oct., 1959, *73*, 560–565. (Address: Department of Radiology, University of California Medical Center, San Francisco 22, Calif.)

This paper is addressed primarily to those contemplating the purchase of equipment for taking roentgen-ray movies. Its aim is to provide information regarding facilities required, the investment in time and money, information obtained with the technique, frequency of its use and its influence on the physician's practice. The cost of installation is usually the first consideration. The basic unit, which includes the ordinary fluoroscopic table with a spot filming device, phototimer, generator and overhead tube with tube stand, lists at approximately $20,000. An intensifying screen will add $6,500 to $12,000 depending on the size of the screen and the manufacturer. Installation of a high grade movie camera with automatic brightness control costs between $5,000 and $6,000. Less expensive units, in the range of $1,000, may be used however. Film processing equipment plus film splicer, viewer and projector bring the total cost to between $35,000 and $45,000.

Of importance in busy departments is the time involved in taking, processing, editing, viewing and

filing the films. Studying the movies alone usually takes an average of one hour per case. This factor in itself may limit the adoption of the technique. The use to which it will be put and the information expected must also be assessed. In its present state, cine-movies find their greatest use in research and teaching. Movies permit the study and restudy of certain functional body movements which are too rapid to be observed by conventional means. Studies of the pharynx in speech and in swallowing, the esophagus and cardioesophageal junction, the heart in angiocardiography, the urinary bladder, and the motion of joints practically constitute the field of usefulness of the cinefluorographic technique. Compared with its assets in teaching and research, the value of cinefluorography in service to patients is small. If a physician sees significant numbers of patients with esophageal, pharyngeal, bladder and joint dysfunction, then cinefluorography may be expected to provide valuable information. But for most private radiology practices it would be of little importance even if twice the existing number of such cases were available.

Finally, the financial yield from cinefluorographic services is extremely small compared with that from fluoroscopy and laminagraphy. A table is presented to show the relative incomes expected from the 3 techniques.

At the present time, therefore, roentgen-ray movies are of tremendous value in teaching and research and they have a small though definite place in the service of selected patients. The investment of funds, time and space, however, is inordinately great when compared to the income that can be derived from its use.—*Z. Petrany, M.D.*

FORMAN, MYRON, BORDEN, ANTHONY BOREADIS, and GERSHON-COHEN, J. Improvement of diagnostic value of photofluorographic films by electronic means; a preliminary report. *Radiology*, Nov., 1959, *73*, 774–775. (Address: M. Forman, Albert Einstein Medical Center, Northern Division, York and Tabor Roads, Philadelphia 41, Pa.)

Because of the difficulty of interpretation of photofluorographic roentgenograms, the use of a Philco Contrast Enhancer was investigated as a method of improving diagnostic quality. The Exicon is a closed television circuit which makes it possible to enlarge the roentgen-ray image and also to change shadings of contrast. The authors chose 70 patients at random for gastrointestinal examination both by conventional means and by photofluorographic technique. In a high percentage of cases an accurate diagnosis was made with photofluorographic methods as compared with regular roentgenograms. It is felt that this makes the method feasible for mass surveys and for teaching.—*James C. Moore, M.D.*

SCHWARZ, GERHART S. Kilovoltage and radiographic effect; investigation leading to a standard x-ray value scale (X.V.S.) system of simplified exposures for conventional and automatic radiography. *Radiology*, Nov., 1959, *73*, 749–761. (Address: 622 W. 168th St., New York 32, N. Y.)

For any proposed roentgenogram of a particular body part there is a certain optimum combination of exposure factors which will yield the best diagnostic quality. On either side of this optimum there is a variable range of exposures which will still result in roentgenograms of adequate diagnostic value. Exposure in photography depends on three prime factors: (a) the shutter speed expressed in seconds; (b) the lens opening expressed in F-stops and; (c) the brightness of the object, *i.e.*, the amount of light reflected by the object. Similarly, in roentgenography the exposure obtained will depend on :(a) timer setting in milliampere seconds; (b) kilovoltage; and (c) the thickness of the patient, which is an approximate expression of the amount of radiation which is transmitted through the subject to the film. In both techniques, the (c) factor is measured or estimated, and from this the (a) and (b) factors are determined either by rote, formula, or from a table.

In photography these determinations have been greatly simplified by the establishment of the so-called "E. V. S." system. This system consists of a set of simple index numbers assigned to each of the possible shutter settings and a similar set of numbers assigned to the lens opening settings. A given sum of any two settings labeled by this system will always give an identical exposure regardless of what the individual settings might be.

An identical system is not possible in roentgenography, however, because of the inconstant relationship of the kilovoltage to the roentgenographic effect. For this reason, the present investigation was carried out in order to determine the actual influence of kilovoltage upon the roentgenographic effect over a wide range of machine settings, and thereby to attempt to establish an exposure system similar to the E. V. S. system of photography.

A masonite bone phantom varying in thickness from 2 to 42 cm. was used. The criteria for a "correct" exposure were those which yielded optimum bone detail. Test exposures were made with varying kilovoltages (28 kv. peak to 133 kv. peak) to determine the exact doubling and halving points for each designated thickness. These readings were plotted on a graph and connected by curves. It was shown that no single exponent for the roentgenographic effect as a function of kilovoltage existed. However, the optimum exposures for each thickness were compared

and the doubling and halving kilovoltages for these exposures were plotted and used as standard points. When joined together, these points formed a "working axis" on either side of which was a range of settings which still yielded adequate exposures.

This zone is broad and covers more machine settings than occur under actual working conditions. It was possible, therefore, to develop a unit system using whole numbers to correspond to the necessary exposure factors as in the E. V. S. system. The caliper used by the technician for measuring patient thickness is labeled to read in roentgen-ray value (X. V.) units. After the body part is measured he sets the three machine controls (kv., ma. and timer) on such index figures that their sum equals the exposure value read off the unit caliper scale. This will effect an acceptable exposure regardless of the individual settings selected and no exposure table need be consulted. Such a caliper and unit system is presented here with tables to show the numerical labeling for the various kv. and mas. settings.

The system, now in actual use, has, in the author's opinion, resulted in a definite decrease in roentgenogram rejects and when error does occur the deviations tend to be small. The adoption of the unit system makes possible the future manufacture and design of much simpler machines with various degrees of automation. One could possibly eliminate kv. and ma. controls entirely and provide a single unalterable setting of these factors. The only variable would be that of the timer which could be set to read identically with the X. V. reading of the caliper. Further degrees of automation are also suggested and described. The final advantage of such a system is that it permits standardization of machine parts, films, and screens, eliminates unnecessary controls, limits error and makes possible partial or complete automation leading eventually to single knob control.—*Z. Petrany, M.D.*

Reeves, John D. Progressive patient care in radiology. *Radiology*, Nov., 1959, *73*, 779–784. (Address: The J. Hillis Miller Health Center, University of Florida, Gainesville, Fla.)

Progressive patient care provides three zones within the hospital where care is tailored to the patient's needs. These three zones or areas are designated: (a) intensive care area for the seriously ill and for immediate postoperative care; (b) intermediate care area for those who need present-day nursing attention; (c) self help area for convalescents and others who may wish to take care of many of their own needs. Better patient care and easing of the economic burden should result.

This concept can be applied to the roentgenologic care of patients in the large hospital, but expert planning is necessary if the full medical and economic benefits of PPC are to be realized. To achieve the best patient care as well as economic operation, a department of radiology should be geographically located in the center of patient distribution. Clinical services most often in need of radiologic consultation, particularly orthopedic surgery and urology, should be located adjacent to radiology.

In planning hospital radiologic facilities, the following important statistical figures are accepted as standard guides: (1) 100 square feet of floor space per patient examined or treated per day, and (2) one roentgen-ray machine per 17 patients examined or treated per day. PPC applied to diagnostic radiology might result in four main radiology patient areas: (a) emergency radiology, (b) special procedures, (c) inpatient area, and (d) ambulatory areas. These four areas could be arranged as the four extremities of the letter "H". An arrangement such as this permits expansion in six directions.—*A. W. Sommer, M.D.*

RADIATION THERAPY

Latourette, H. B., Simons, C. S., and Lampe, I. A localization scheme for radiation therapy planning with the theratron. *Radiology*, Nov., 1959, *73*, 762–770. (Address: H. B. Latourette, University Hospitals, Iowa City, Iowa.)

The authors describe a system for lesion localization and beam direction utilizing preliminary anteroposterior and lateral radiographs incorporating "ruler" reference markers. The patient is usually placed in supine position on the treatment table, which is covered by a full length foam rubber pad 1 in. thick. All irradiation prescriptions consequently contain, as one of the coordinates of beam direction, the distance from the plane of the couch top to the central ray of the horizontal beam. A second coordinate is the distance, cephalad or caudad, from some prominent anatomic landmark. The third coordinate is the distance laterally from the midline.

A lateral radiograph is made using a cassette holder with opaque reference marks near its center. The patient is then removed from the table and a vertical ruler with opaque centimeter scale markings is placed in the exact center of the patient's former position. When these opaque reference marks on the two developed lateral films are superimposed, the distance from the table top to the point of interest in the patient can be read directly from the "ruler" radiograph. A similar method is used for the anteroposterior film. If rotation therapy is to be used, the patient's contour is traced on paper by the wire solder method, and localization by "ruler" radiograph is then carried out as described.

The accuracy of the localization is verified at the first treatment session by obtaining radiographs with cobalt 60 gamma rays. A special head holder used

both for localization and for positioning during therapy is described.—*John S. Alexander, M.D.*

EMERY, E. W., LUCAS, B. G. B., and WILLIAMS, K. G. Technique of irradiation of conscious patients under increased oxygen pressure. *Lancet*, Jan. 30, 1960, *1*, 248–250. (From: University College Hospital, London, W.C.1, England.)

In order to take advantage of the well-known principle that radiosensitivity of the cell is enhanced by an increase in oxygen tension, a compression chamber was built. The transparent chamber allows visual and auditory contact with the patient and eliminates much of the apprehension present when the patient is treated in a metal chamber. Incorporated in the apparatus is a system of pressurization which will minimize ear and sinus pain, ventilation to prevent retention of water vapor and carbon dioxide, and a double walled cylinder to eliminate the risk of explosive decompression. Total time of one treatment is usually less than half an hour. The authors hope to develop the technique so that it can be used for treating conscious patients at pressures up to four atmospheres absolute.—*Roger D. Cornell, M.D.*

DEGINDER, W. L., and LOVELL, B. K. Accelerated palliative radiation therapy of bronchial carcinoma with 250-kv. roentgen rays. *Radiology*, Nov., 1959, *73*, 684–692. (Address: W. L. DeGinder, Austin Radiological Group, 2410 Rio Grande, Austin 5, Texas.)

The authors report the results of a study of accelerated palliative radiation therapy of bronchial carcinoma with 250 kv. roentgen rays. Since 1946, approximately 560 patients have received 230 kv. or 260 kv. palliative therapy for primary bronchial carcinoma in the Dallas and McKinney Veterans Administration Hospitals. After exclusion of patients with unconfirmed diagnosis, incomplete follow-up, and those treated only for distant metastases, 446 cases remained for study.

The total dose was based on the predicted moist desquamation threshold. The factors were 250 kv. peak, 2.5 mm. Cu half value layer, 50 cm. target skin distance. Two opposite portals of 9×12 cm. were used. In eight days elapsed time, 3,600 r was delivered to each area in 6 treatments of 400 r (in air) each, or treatment was extended over fourteen days, with 4,000 r to each skin area in 10 treatments of 260 r (in air) each. The exit skin dose without back scatter was estimated to be 20 per cent. The tumor doses ranged from 1,500 r to 3,200 r.

Survivals in this report are considered only in relation to the period of possible benefit from the palliative treatment, namely, that period beginning with the institution of treatment. With the accelerated palliative therapy, 21 per cent survived one year or more. Ninety-seven patients were able to resume work for some period of time after treatment. Only forty-eight patients treated by the accelerated method were unable to return to home care within a month from the start of treatment.

The importance of a close physician-patient relationship is stressed. Relief of anxiety and the creation of hope contribute to the patient's subjective improvement. The accelerated treatment and early discharge from the hospital are active factors in the improvement of patient morale and a reduction of complaints. It is therefore difficult to make an accurate subjective evaluation of palliative results, but accelerated therapy does result in satisfactory palliation without producing painful sequelae to skin, pleura, or lung.—*A. W. Sommer, M.D.*

RUBENFELD, SIDNEY, and KAPLAN, GUSTAVE. Treatment of bronchogenic cancer with conventional x-rays according to a specific time-dose pattern. *Radiology*, Nov., 1959, *73*, 671–678. (Address: S. Rubenfeld, 477 First Ave., New York 16, N. Y.)

Forty-three consecutive patients with histologically proved cancer of the lung were treated with conventional roentgen-ray therapy according to a uniform, abbreviated time-dose pattern. Treatments were given with roentgen-rays generated at 250 kv., Thoraeus II filter, half value layer 1.25 mm. Cu at 50 cm. distance. The size of the field varied from 10×10 to 10×15 cm. All lesions received a calculated tumor dose of 3,000 r in fourteen elapsed days. The skin doses ranged from 4,000 r to 4,800 r.

The ages of the patients ranged from thirty-nine to seventy-three years. All tumors were histologically proved. All but 2 of the patients had distant metastases detected clinically, roentgenologically or at thoracotomy. The symptoms were controlled in 72 per cent of the series. Objective improvement was noted in 43 per cent of the patients. The most common symptoms to be alleviated were as follows: hemoptysis, 15 cases; pain, 14 cases; cough, 10 cases; dyspnea, 5 cases; superior vena cava syndrome, 1 case. There was no need to interrupt treatments because of radiation sickness, tracheitis, esophagitis, or skin reaction.

The abbreviated time-dose pattern achieved satisfactory palliation, shortened the hospitalization period, and did not induce serious debilitation.—*A. W. Sommer, M.D.*

LOUGHEED, M. N., and MAGUIRE, G. H. Irradiation pneumonitis in the treatment of carcinoma of the breast. *J. Canad. A. Radiologists*, Mar., 1960, *21*, 1–10. (From: Montreal General Hospital, Montreal, Quebec, Canada.)

In irradiating lesions of the chest wall, it is at times impossible to prevent irradiation of pulmonary tissue. This paper deals with the incidence, correlated factors, and morbidity of these pulmonary changes in the treatment of cancer of the breast.

In the years 1953 to 1957, 491 new cases of breast carcinoma were seen. Of these, 255 received radiation therapy as follows: primary quadrate treatment, 94; postoperative irradiation to node bearing areas, 91; and to metastatic areas, 70.

The quadrate radiation technique includes fields directed tangentially to the breast, chest wall, axilla, and anterior mediastinum. Bolus is used. This large area is treated to tissue tolerance with 250 kv. peak, half value layer 2–2.4 mm. Cu at 50 cm. focus skin distance. The time varies from ten to twelve weeks.

The postoperative irradiation includes an anteroposterior mediastinal field 9 cm. × 18 cm., an anteroposterior supraclavicular field 8 cm. × 16 cm., and an axillary field 19 cm. × 10 cm. A combination of 250 kv. peak and Co^{60} teletherapy is used. Treatment time is six to seven weeks.

The diagnosis of radiation pneumonitis is based on such clincal features as low-grade fever, prostration, dyspnea on exertion, nonproductive cough, and tachycardia. The roentgenographic changes include a coarse reticular or patchy infiltration, contraction of the lung, tenting of the diaphragm, absence of pleural effusion, and correlation of irradiation with the distribution of the pulmonary pathology.

The clinical features usually occur about one to four weeks after treatment. The roentgen changes are observed seven to ten weeks after treatment.

In the quadrate therapy group, 61 per cent had roentgen changes attributable to radiation. The average dose to those with pulmonary changes was 6,500 to 7,000 r in ten to eleven weeks.

In the postoperative irradiation group, 37 per cent had changes attributable to radiation. The average dose was 6,500 r in seven weeks to the lung apex. The extent of lung changes in this group was considerably less than in the quadrate therapy group.

If there is a critical level below which pneumonitis does not occur, it is probably between 2,500 and 3,400 r in seven weeks.

Of the 59 cases including both groups only 5 showed partial resolution of the radiation changes.

The authors briefly discuss the pathology of the process and point out the nonspecific histologic lung changes.

The lung alterations are usually asymptomatic. Less than 4 per cent produce symptoms. ACTH and cortisone were used in treating this small group of patients. The authors claim prompt relief of symptoms in the mild cases. Success or failure, however, should not be based on the return to normal of the chest roentgenogram, although steroid therapy may reduce changes that have already developed.—*Gerald J. Kurlander, M.D.*

Gish, James R., Coates, E. O., DuSault, Lucille A., and Doub, Howard P. Pulmonary radiation reaction: a vital-capacity and time-dose study. *Radiology*, Nov., 1959, *73*, 679–683. (Address: J. R. Gish, 317 Goodhue Building, Beaumont, Texas.)

The object of this paper is to report a study of the relationship of the time-dose aspect of radiation therapy to radiation induced fibrosis and of pulmonary vital capacity as an index of lung function in those patients with fibrosis. The study includes a group of cases with adequate roentgenologic and clinical follow-up in which the lungs received incident radiation during therapy to the mediastinum, lungs, and node-bearing areas of the chest wall. In those cases in which reactions appeared, vital capacity studies were made. The pulmonary radiation reactions were classified into four groups as follows: I, pleural reaction only; II, pneumonitis—soft fluffy lesion, usually clearing within six months; III, pneumonitis clearing in from six months to a year and leaving moderate linear fibrotic residue; IV, pneumonitis clearing in from six months to a year and leaving extensive fibrotic residue. Irradiation was administered by means of roentgen therapy with half value layer of 1 to 3 mm. Cu or by cobalt teletherapy. The maximal dose to the lung varied from 2,000 to 8,200 r in periods covering five to eighty-two days.

Measurements of the total and three second vital capacities were made prior to treatment and subsequently in 24 patients. Any reduction in vital capacity, which in most instances was present three months after the beginning of radiation therapy, was not large in any case. None of the patients studied in this way showed any clinical signs of impaired pulmonary function. Decreased vital capacity seemed to correlate better with presence of disease in the patient as shown by later metastasis than with reports of fibrosis on the roentgenogram.

Pleuropulmonary reactions occurred in 44 per cent of those patients receiving 250 kv. roentgen therapy but in only 20 per cent of those receiving cobalt 60 therapy, although in general the latter group received a higher tissue dose. Some degree of pleuropulmonary reaction was demonstrated in 18 of 44 patients whose lungs were exposed peripherally; however, out of 10 patients who were treated over the mediastinum and medial borders of the lungs, a reaction was observed in only 1. There were few instances of pleuropulmonary reaction in patients irradiated tangentially. The incidence of reaction was about twice as great for field sizes of 15 × 20 cm. or larger than for 10 × 15 cm. ports or smaller.

Time-dose data for the groups showing some permanent residual fibrosis (III and IV) and for the groups showing temporary reaction only (I and II) were plotted on log-log paper, and a line representing the incidence of fibrosis was drawn below those points

in the first group. The dose level of about 3,700 r in twenty-nine days seems fairly definite. No distinction in results could be made between 250 kv. and cobalt 60 therapy, although most of the points above the line indicating temporary reaction only are from the cobalt group. The incidence of pulmonary reaction as previously described, 44 per cent for roentgen therapy and 20 per cent for cobalt therapy, suggests that the time-dose line for roentgen therapy may be lower. In a review of the literature, time-dose values consistent with this lung tolerance line were reported when similar techniques were used; with other techniques there was fibrosis following widely scattered time-dose combinations.—*W. H. Jarvis, Jr., M.D.*

Kolář, J., and Vrabec, R. Ungewöhnliche Knochenschädenformen nach der Bestrahlung im Beckenbereich. (Unusual bone damages following radiation treatment to the pelvic region.) *Radiol. clin.*, Mar., 1960, *29*, 109–116. (Address: J. Kolář, Radiologische Klinik SFN 1, U nemocnice 2, Prague, Czechoslovakia.)

The authors describe unusual findings and localizations of radiation damage to the innominate bones and the sacrum following radiation therapy for various pathologic conditions in the pelvis, usually malignant ones. They emphasize that the precursor of spontaneous fractures is an area of diminished bone density, sometimes combined with sclerotic changes. This can be seen not only in the neck of the femur but also in the pubic, ischial and sacral bones. This is of practical importance, as such findings can be easily confused on roentgenography with other pathologic conditions, especially bone metastases. Furthermore, this damage appears in women as well as in men who have undergone pelvic irradiation.—*Eckart Schackow, M.D.*